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IBM Technical Disclosure Bulletins

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USPT,JPAB,EPAB,DWPI	((536/23.1  536/23.5  536/23.51  536/24.1 )!.CCLS. )	7704	<u>L3</u>
USPT,JPAB,EPAB,DWPI	((435/455  435/467  435/325  435/368 )!.CCLS. )	3527	<u>L2</u>
USPT,JPAB,EPAB,DWPI	((800/8  800/9  800/10  800/13  800/18  800/21  800/22  800/25 )!.CCLS. )	324	<u>L1</u>

\*\*\*\*\* \$TN Columbus \*\*\*\*\*

FILE 'HOME' ENTERED AT 09:24:45 ON 21 SEP 2000

=> file medline

COST IN U.S. DOLLARS	ENTRY	SINCE FILE	TOTAL
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FILE 'MEDLINE' ENTERED AT 09:24:53 ON 21 SEP 2000

FILE LAST UPDATED: 15 SEP 2000 (20000915/UP). FILE COVERS 1960 TO DATE.

MEDLINE has been reloaded to reflect the annual MeSH changes made by the National Library of Medicine for 2000. Enter HELP RLOAD for details.

The OLD MEDLINE file segment now contains data from 1958 through 1965. Enter HELP CONTENT for details.

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THIS FILE CONTAINS CAS REGISTRY NUMBERS FOR EASY AND ACCURATE SUBSTANCE IDENTIFICATION.

=> s neuronal/ab,bi

80711 NEURONAL/BI  
5413360 AB/FA  
66007 NEURONAL/AB  
(NEURONAL/BI (L) AB/FA)  
80711 NEURONAL/BI  
L1 80711 NEURONAL/AB,BI

=> s 11 and (transfect? or transfect?) /ab,bi

70593 TRANSFECT/BI  
5413360 AB/FA  
45486 TRANSFECT/AB  
(TRANSFECT/BI (L) AB/FA)  
70593 TRANSFECT/BI  
214836 TRANSFORM/BI  
5413360 AB/FA  
107557 TRANSFORM/AB  
(TRANSFORM/BI (L) AB/FA)

214836 TRANSFORM/BI  
91974 TRANSFECT/BI  
5413360 AB/FA  
49924 TRANSFECT/AB  
(TRANSFECT/BI (L) AB/FA)  
91974 TRANSFECT/BI  
L2 5827 L1 AND (TRANSFECT? OR TRANSFORM? OR TRANSFECT?/AB,BI

=> s 12 and toxin#/ab,bi

58774 TOXIN/BI  
5413360 AB/FA  
39784 TOXIN/AB  
(TOXIN/BI (L) AB/FA)  
58774 TOXIN/BI  
L3 180 L2 AND TOXIN#/AB,BI

=> s 13 and vivo/ab,bi

267353 VIVO/BI  
5413360 AB/FA  
230827 VIVO/AB  
(VIVO/BI (L) AB/FA)  
267353 VIVO/BI  
L4 18 L3 AND VIVO/AB,BI

=> d 1- bib ab

YOU HAVE REQUESTED DATA FROM 18 ANSWERS - CONTINUE? Y(N)y

L4 ANSWER 1 OF 18 MEDLINE  
AN 1999343779 MEDLINE  
DN 99343779  
TI Chemokine receptor expression and signaling in macaque and human fetal neurons and astrocytes: implications for the neuropathogenesis of AIDS.  
AU Klein R S; Williams K C; Alvarez-Hernandez X; Westmoreland S; Force T;  
Lackner A A; Luster A D  
CS AIDS Research Center, Massachusetts General Hospital, Harvard Medical School, Charlestown 02129, USA. klein.robym@mgh.harvard.edu  
NC A01519 (NIAID)  
CA69212 (NCI)  
A140618 (NIAID)  
+  
SO JOURNAL OF IMMUNOLOGY, (1999 Aug 1) 163 (3) 1636-46.

Journal code: IFB. ISSN: 0022-1767.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Abridged Index Medicus Journals; Priority Journals; Cancer

Journals  
EM 199910  
EW 19991002  
AB Chemokines are believed to play a role in the neuropathogenesis of AIDS through their recruitment of neurotoxin-secreting, virally infected leukocytes into the CNS. Levels of chemokines are elevated in brains of patients and macaques with HIV/SIV-induced encephalitis. The chemokine receptors CCR3, CCR5, and CXCR4 are found on subpopulations of neurons in the cortex of human and macaque brain. We have developed an in vitro system using both macaque and human fetal neurons and astrocytes to further investigate the roles of these receptors in \*\*\*neuronal\*\*\* response to inflammation. Here we report the presence of functional HIV/SIV coreceptors CCR3, CCR5, and CXCR4 on fetal human neurons and CCR5 and CXCR4 on astrocytes immediately ex \*\*\*vivo\*\*\* and after several weeks in culture. Confocal imaging of immunostained neurons demonstrated different patterns of distribution for these receptors, which may have functional implications. Chemokine receptors were shown to respond to their appropriate chemokine ligands with increases in intracellular calcium that, in the case of neurons, required depolarization with KCl. These responses were blocked by neutralizing chemokine receptor in mAbs. Pretreatment of neural cells with pertussis \*\*\*toxin\*\*\* abolished responses to stromal-derived factor-1 alpha, macrophage inflammatory protein-1 beta, and RANTES, indicating coupling of CCR5 and CXCR4 to a Gialpha protein, as in leukocytes. Cultured macaques demonstrated calcium flux response to treatment with recombinant SIVmac239 envelope protein, suggesting a mechanism by which viral envelope could affect \*\*\*neuronal\*\*\* function in SIV infection. The presence of functional chemokine receptors on neurons and astrocytes suggests that chemokines could serve to link inflammatory and \*\*\*neuronal\*\*\* responses.

L4 ANSWER 2 OF 18 MEDLINE  
AN 1999253888 MEDLINE  
DN 99253888  
TI GDNF: a novel factor with therapeutic potential for

neurodegenerative disorders.

AU Walton K M  
CS Department of Neurobiology, Cephalon, Inc., West Chester, PA 9380, USA.

SO MOLECULAR NEUROBIOLOGY, (1999 Feb) 19 (1) 43-59.  
Journal code: AH6. ISSN: 0893-7648.

CY United States

DT Journal: Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199908

AB The identification of novel factors that promote

\*\*\*neural\*\*\*

survival could have profound effects on developing new

therapeutics for neurodegenerative disorders. Glial cell line-derived neurotrophic factor (GDNF) is a novel protein purified and cloned based on its marked ability

to promote dopaminergic \*\*\*neural\*\*\* function. GDNF, now known to be the first identified member of a family of factors, signals through

previously known receptor tyrosine kinase, Ret. Unlike most

ligands for receptor tyrosine kinases, GDNF does not bind and activate Ret directly, but requires the presence of GPI-linked coreceptors. There are several

coreceptors with differing affinities for the GDNF family members. The profile of coreceptors in a cell may determine which factor

preferentially activates Ret. In \*\*\*vivo\*\*\* differences in localization of the GDNF

family members, its coreceptors and Ret suggest this ligand/receptor

interaction has extensive and multiple functions in the CNS as well as in peripheral tissues. GDNF promotes survival of several

\*\*\*neural\*\*\*

populations both in vitro and in \*\*\*vivo\*\*\*. Dopaminergic

\*\*\*neural\*\*\* survival and function are preserved by GDNF

in

\*\*\*vivo\*\*\* when challenged by the \*\*\*toxins\*\*\* MPTP and

6-hydroxydopamine. Furthermore, GDNF improves the symptoms

of pharmacologically induced Parkinson's disease in monkeys. Several neuron populations isolated in vitro are also rescued by GDNF. In

\*\*\*vivo\*\*\*, GDNF protects these neurons from programmed cell death

associated with development and death induced by

\*\*\*neural\*\*\*

transfection. These experiments suggest that GDNF may provide significant

therapeutic opportunities in several neurodegenerative disorders.

L4 ANSWER 3 OF 18 MEDLINE

AN 1999198837 MEDLINE

DN 99198837

TI Melatonin receptor potentiation of cyclic AMP and the cystic fibrosis

transmembrane conductance regulator ion channel.

AU Nelson C S; Marino J L; Allen C N

CS Center for Research on Occupational and Environmental

Toxicology,

Department of Psychiatry, Oregon Health Sciences University,

Portland

97201, USA.

NC AG10794 (NIA)

SO JOURNAL OF PINEAL RESEARCH, (1999 Mar) 26 (2)

113-21.

Journal code: JND. ISSN: 0742-3098.

CY Denmark

DT Journal: Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199907

EW 19990704

AB We have used the cystic fibrosis transmembrane conductance

regulator (CFTR) Cl<sup>-</sup> channel as a model system to study the cAMP signal

\*\*\*transduction\*\*\* pathways coupled to the Xenopus melatonin

receptor.

During forskolin (Fsk) stimulation, melatonin reduced the

amplitude of the

CFTR currents in oocytes injected with in vitro transcribed cRNAs

for the

Xenopus melatonin receptor and CFTR. Pertussis \*\*\*toxin\*\*\*

(Ptx) treatment eliminated melatonin inhibition of Fsk stimulated CFTR

currents.

In oocytes injected with cRNA for melatonin receptors, serotonin

receptors

(5-HT<sub>7</sub>), and CFTR Cl<sup>-</sup> channels, application of melatonin together

with

serotonin (5-HT) activated an additional inward current showing

potentiation of adenylyl cyclases by melatonin receptors.

Subthreshold

activation of 5-HT<sub>7</sub> receptors was sufficient and necessary to

permit

activation of CFTR channels by melatonin. Preexposure to

melatonin

desensitized the melatonin receptor mediated response. Therefore,

based on

this model system, the effects of melatonin in \*\*\*vivo\*\*\* could

be

either positive or negative modulation of other \*\*\*neural\*\*\*

inputs,

depending on the mode of adenylyl cyclase stimulation.

L4 ANSWER 4 OF 18 MEDLINE

AN 1999192822 MEDLINE

DN 99192822

TI Non-viral \*\*\*neural\*\*\* gene delivery mediated by the HC

fragment of

tetanus \*\*\*toxin\*\*\*

AU Knight A; Carvajal J; Schneider H; Coutelle C; Chamberlain S;

Fairweather

N

CS Section of Molecular Genetics, ICSM, London, UK.

am.knight@ic.ac.uk

SO EUROPEAN JOURNAL OF BIOCHEMISTRY, (1999 Feb)

259 (3) 762-9.

Journal code: EMZ. ISSN: 0014-2956.

CY GERMANY; Germany, Federal Republic of

DT Journal: Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199906

EW 19990604

AB Many inherited neurological diseases and cancers could

potentially benefit

from efficient targeted gene delivery to neurons of the central

nervous

system. The nontoxic fragment C (HC) of tetanus \*\*\*toxin\*\*\*

retains

the specific nerve cell binding and transport properties of tetanus

holotoxin. The HC fragment has previously been used to promote

the uptake

of attached proteins such as horseradish peroxidase,

beta-galactosidase

and superoxide dismutase into \*\*\*neural\*\*\* cells in vitro and

in

\*\*\*vivo\*\*\*. We report the use of purified recombinant HC

fragment

produced in yeast and covalently bound to polylysine [poly(K)] to

enable

binding of DNA. We demonstrate that when used to

\*\*\*transfect\*\*\*

cells, this construct results in nonviral gene delivery and marker

gene

expression in vitro in N18 RE 105 cells (a neuroblastoma x glioma

mouse/rat hybrid cell line) and F98 (a glioma cell line).

\*\*\*Transfection\*\*\* was dependent on HC and was

\*\*\*neural\*\*\* cell

type specific. HC may prove a useful targeting ligand for future

\*\*\*neural\*\*\* gene therapy.

L4 ANSWER 5 OF 18 MEDLINE

AN 1999126974 MEDLINE

DN 99126974

TI Pituitary adenylate cyclase activating peptide (PACAP) in the

retinohypothalamic tract: a daytime regulator of the biological

clock.

AU Hannibal J; Ding J M; Chen D; Fahrenkrug J; Larsen P J;

Gillette M U;

Mikkelsen J D

CS Department of Clinical Biochemistry, Bispebjerg Hospital,

University of Copenhagen, Denmark. biochbbh@inet.uni2.dk  
 NC NS22155 (NINDS)  
 SO ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (1998 Dec 11) 865 197-206.  
 Journal code: 5NM. ISSN: 0077-8923.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals; Cancer Journals  
 EM 199904  
 EW 19990403  
 AB The retinohypothalamic tract (RHT) relays photic information from the eyes to the brain biological clock in the suprachiasmatic nucleus (SCN). Activation of this pathway by light plays a role in adjusting circadian timing to light exposure at night. Here we report a new signaling pathway by which the RHT regulates circadian timing in the daytime as well. Using dual-immunocytochemistry for PACAP and the in \*\*\*vivo\*\*\* tracer Cholera \*\*\*toxin\*\*\* subunit B (ChB), intense PACAP immunoreactivity was observed in retinal afferents at the rat SCN as well as in the intergeniculate leaflet (IGL) of the thalamus. This PACAP-IR was nearly lost upon bilateral eye enucleation. PACAP afferents originated from ganglion cells distributed throughout the retina. The phase of circadian rhythm measured as SCN \*\*\*neuronal\*\*\* activity in vitro was significantly advanced by application of PACAP-38 during the subjective day, but not at night. The effect is channelled to the clock via a PACAP 1 receptor-cAMP signaling mechanism. Thus, in addition to its role in nocturnal regulation by glutamatergic neurotransmission, the RHT can adjust the biological clock by a PACAP-cAMP-dependent mechanism during the daytime.

L4 ANSWER 6 OF 18 MEDLINE  
 AN 1999066984 MEDLINE  
 DN 99066984  
 TI LIF (AM424), a promising growth factor for the treatment of ALS.  
 AU Kurek J B; Radford A J; Crump D E; Bower J J; Feeney S J; Austin L; Byrne E  
 CS AMRAD Corporation Ltd, Melbourne, Australia.  
 jkurek@amrad.com.au  
 SO JOURNAL OF THE NEUROLOGICAL SCIENCES, (1998

Ox) 160 Suppl 1 S106-13.  
 Ref: 64  
 Journal code: JBI. ISSN: 0022-510X.  
 CY Netherlands  
 DT Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW, TUTORIAL)  
 LA English  
 FS Priority Journals  
 EM 199905  
 EW 19990503  
 AB Growth factors are theoretically promising agents for ALS therapy, but have been disappointing in subcutaneous delivery due to either toxicity or lack of major efficacy. Leukaemia inhibitory factor (LIF), was named after its effect on haemopoietic cells, and belongs to a group of cytokines which includes CNTF, IL-6, CT-1, OM and IL-11. All group members use the gp130 signal \*\*\*transducing\*\*\* subunit for intracellular signalling, but show differences in biological effect. In vitro and in \*\*\*vivo\*\*\* studies on axotomy and nerve crush models demonstrate a powerful effect of LIF in the survival of both motor and sensory neurones, while reducing denervation induced muscle atrophy. Its effects in muscle also include stimulating myoblast proliferation in vitro, and up-regulation after muscle injury. LIF will also stimulate muscle regeneration in \*\*\*vivo\*\*\* when applied exogenously after injury. In published studies of both axotomy induced \*\*\*neuronal\*\*\* death and in the Wobbler mouse models LIF is active at doses of 10 microg/kg delivered systemically, well below the expected maximum tolerated dose suggested by primate safety studies. LIF is expressed in low levels by spinal cord neurones with significant up-regulation when the neurones are damaged by BOAA \*\*\*toxin\*\*\*, an excitatory amino acid associated with a form of ALS. This evidence suggesting LIF is a trauma factor playing a role in the response of adult \*\*\*neuronal\*\*\* tissue, and may be more effective than related growth factors. Taken together, the data suggests LIF is a physiologically relevant trophic factor with implications in clinical medicine as a therapy for ALS, and a human recombinant form entered human clinical trials during 1998.

L4 ANSWER 7 OF 18 MEDLINE  
 AN 1998453369 MEDLINE  
 DN 98453369  
 TI Landmarks in the application of 13C-magnetic resonance spectroscopy to studies of \*\*\*neuronal\*\*\* /glial relationships.  
 AU Bachelard H  
 CS MR Centre, Department of Physics, University of Nottingham, UK.  
 pzwbx@ppm1.not.ac.uk  
 SO DEVELOPMENTAL NEUROSCIENCE, (1998) 20 (4-5) 277-88. Ref: 70  
 Journal code: ECS. ISSN: 0378-5866.  
 CY Switzerland  
 DT (LECTURES)  
 General Review; (REVIEW)  
 (REVIEW, TUTORIAL)  
 LA English  
 FS Priority Journals  
 EM 199903  
 EW 19990301  
 AB The development of the use of carbon isotopes as metabolic tracers is briefly described. 13C-labelled precursors (13CO2, 13CH4) first became available in 1940 and were studied in microorganisms, but their use was limited by very low enrichments and lack of suitable analytical equipment. More success was achieved with 11C and especially 14C, as these radioactive tracers did not need to be highly enriched. Although the stable 13C isotope can be used at a low percentage enrichment in mass spectrometry, its application to magnetic resonance spectroscopy (MRS) requires very highly enriched precursors, due to its low natural abundance and low sensitivity. Despite such limitations, however, the great advantage of 13C-MRS lies in its exquisite chemical specificity, in that labelling of different carbon atoms can be distinguished within the same molecule. Effective exploitation became feasible in the early 1970s with the advent of stable instruments, Fourier \*\*\*transform\*\*\* 13C-MRS, and the availability of highly enriched precursors. Reports of its use in brain research began to appear in the mid-1980s. The applications of 13C isotope analysis to research on \*\*\*neuronal\*\*\* /glial relationships are reviewed. The presence of neighbouring 13C-labelled atoms affects the appearance of the resonances (splitting due to C-C coupling), and so allows for unique quantification of rates through different and possibly

competing pathways. Isotopomer patterns in resonances labelled from a combination of [1-13C]glucose and [1, 2-13C]acetate have revealed aspects of \*\*\*neural\*\*\* glial metabolic trafficking on depolarization and under hypoxic conditions in vitro. This approach has now been applied to in \*\*\*vivo\*\*\* studies on inhibition of glial metabolism using fluoracetate. The results confirm the glial specificity of the \*\*\*toxin\*\*\* and demonstrate that it does not affect entry of acetate. When the glial TCA cycle is inhibited, the ability of the glia to participate in the glutamate/glutamine cycle remains unimpaired, in that labelling of glutamine, which can only be derived from \*\*\*neural\*\*\* metabolism of glucose, persists. The results also confirmed earlier evidence that part of the GABA transmitter pool is derived from glial glutamine.

L4 ANSWER 8 OF 18 MEDLINE  
AN 1998082844 MEDLINE  
DN 98082844  
TI Contributions of N-linked glycosylation to the expression of a functional alpha7-nicotinic receptor in *Xenopus* oocytes.  
AU Chen D; Dang H; Patrick J W  
CS Division of Neuroscience, Baylor College of Medicine, Houston, Texas 77030, USA.  
NC NS13546 (NINDS)  
DA04077 (NIDA)  
SO JOURNAL OF NEUROCHEMISTRY, (1998 Jan) 70 (1) 349-57.  
Journal code: JAV. ISSN: 0022-3042.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199804  
EW 19980401  
AB The alpha7 subunit of the \*\*\*neural\*\*\* nicotinic acetylcholine receptor, when expressed in *Xenopus* oocytes, forms homooligomeric ligand-gated ion channels that are blocked by a snake \*\*\*toxin\*\*\*. The amino-terminal extracellular domain of the alpha7 sequence has three consensus sites for asparagine-linked glycosylation (N46DS, N90MS, and N133AS). In this study, we show that alpha7 expressed either in \*\*\*vivo\*\*\* or in vitro is a glycoprotein of 57 kDa. In addition, we demonstrate by site-directed mutagenesis that all three

consensus sites are used for glycosylation. To elucidate the role(s) of asparagine-linked glycosylation in the formation and function of the alpha7 receptor, wild-type and glycosylation-deficient alpha7 subunits were expressed in COS cells and oocytes. We examined biochemical and physiological properties of expressed receptors and found that alpha7 glycosylation mutations do not affect homooligomerization and surface protein expression of the alpha7 receptor but do affect surface expression of alpha-bungarotoxin binding sites and the function of the receptor. Our data indicate that asparagine-linked glycosylation is required for the expression of a functional alpha7 receptor in oocytes.

L4 ANSWER 9 OF 18 MEDLINE  
AN 97360034 MEDLINE  
DN 97360034  
TI Neurotoxicity of soluble macrophage products in vitro--influence of dexamethasone.  
AU Flavin M P; Ho L T; Coughlin K  
CS Department of Pediatrics, Queen's University, Kingston, Ontario, Canada.  
SO EXPERIMENTAL NEUROLOGY, (1997 Jun) 145 (2 Pt 1) 462-70.  
Journal code: EQF. ISSN: 0014-4886.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199710  
EW 19971001  
AB When macrophage conditioned medium is added to neurons in vitro, there is a loss of cell membrane integrity, a loss of cell processes, and a large increase in apoptotic neurons. We tested the influence of a potent anti-inflammatory steroid on the interaction between macrophages and neurons. Dexamethasone was applied to macrophages in culture for 24 h while the culture was stimulated with lipopolysaccharide and hypoxia. Conditioned medium was collected after dexamethasone was removed. The dexamethasone pretreated medium was not toxic to hippocampal neurons in contrast to medium from stimulated macrophages not treated with steroid. The dexamethasone effect was concentration dependent. Pretreatment of macrophages with indomethacin and \*\*\*transforming\*\*\* growth factor

beta had similar but less impressive effects when compared to dexamethasone. The effect of dexamethasone may have been mediated by inhibiting the synthesis or release of neurotoxic macrophage protein(s), as a combination of medium from steroid pretreated macrophages with medium from nontreated macrophages was not neuroprotective. The \*\*\*toxin\*\*\* (s) did not appear to be tumor necrosis factor alpha or arginase. A role for most neutral proteases was also excluded. We also assessed the consequence of stressing neurons with a mild hypoxic exposure immediately prior to conditioned medium application. Medium from dexamethasone-treated macrophages did not exaggerate hypoxic \*\*\*neural\*\*\* injury, unlike medium from non-dexamethasone-treated macrophages. It did not, however, block the exaggerating effect when coapplied in equal volume with medium from nontreated macrophages. Dexamethasone at 100 nM had no impact when applied directly to neurons while they were being exposed to conditioned medium. This in vitro protection by dexamethasone may be relevant to the demonstrated benefit of glucocorticoids in selected brain and spinal cord conditions. Suspicion of a potential link between this in vitro finding and in \*\*\*vivo\*\*\* CNS injury justifies an assessment of more specific agents acting on macrophage protein synthesis or secretion.

L4 ANSWER 10 OF 18 MEDLINE  
AN 97218291 MEDLINE  
DN 97218291  
TI Pituitary adenylate cyclase-activating peptide (PACAP) in the retinohypothalamic tract: a potential daytime regulator of the biological clock.  
AU Hannibal J; Ding J M; Chen D; Fahrenkrug J; Larsen P J; Gillette M U; Mikkelsen J D  
CS Department of Clinical Biochemistry, Bispebjerg Hospital, University of Copenhagen, DK-2400 Copenhagen NV, Denmark.  
NC NS22155 (NINDS)  
SO JOURNAL OF NEUROSCIENCE, (1997 Apr 1) 17 (7) 2637-44.  
Journal code: JDF. ISSN: 0270-6474.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals

EM 199904  
 EW 19990404  
 AB The retinohypothalamic tract (RHT) relays photic information from the eyes to the suprachiasmatic nucleus (SCN). Activation of this pathway by light plays a role in adjusting circadian timing via a glutamatergic pathway at night. Here we report a new signaling pathway by which the RHT may regulate circadian timing in the daytime as well. We used dual immunocytochemistry for pituitary adenylylate cyclase-activating peptide (PACAP) and the in **\*\*\*vivo\*\*\*** tracer cholera **\*\*\*toxin\*\*\*** subunit B and observed intense PACAP-immunoreactivity (PACAP-IR) in afferents in the rat SCN as well as in the intergeniculate leaflet (IGL) of the thalamus. This PACAP-IR in the SCN as well as in the IGL was nearly lost after bilateral eye enucleation. PACAP afferents originated from small ganglion cells distributed throughout the retina. The phase of circadian rhythm measured as SCN **\*\*\*neuronal\*\*\*** activity in vitro was significantly advanced ( $3.5 \pm 0.4$  hr) by application of  $1 \times 10^{-6}$  M PACAP-38 during the subjective day [circadian time (CT)-6] but not at night (CT14 and CT19). The phase-shifting effect is channeled to the clock via a PACAP-R1 receptor, because mRNA from this receptor was demonstrated in the ventral SCN by *in situ* hybridization. Furthermore, vasoactive intestinal peptide was nearly 1000-fold less potent in stimulating a phase advance at CT6. The signaling mechanism was through a cAMP-dependent pathway, which could be blocked by a specific cAMP antagonist, Rp-cAMPS. Thus, in addition to its role in nocturnal regulation by glutamatergic neurotransmission, the RHT may adjust the biological clock by a PACAP/cAMP-dependent mechanism during the daytime.

L4 ANSWER 11 OF 18 MEDLINE  
 AN 97157369 MEDLINE  
 DN 97157369  
 TI Calcium in suramin-induced rat sensory neuron toxicity in vitro.  
 AU Sun X; Windbank A J  
 CS Department of Neurology, Mayo Clinic and Mayo Foundation, Rochester, MN 55905, USA.  
 NC NS29769 (NINDS)  
 SO BRAIN RESEARCH, (1996 Dec 2) 742 (1-2) 149-56.  
 Journal code: BSL. ISSN: 0006-8993.

CY Netherlands  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199706  
 EW 19970604  
 AB Suramin is an experimental chemotherapeutic agent and a neurotoxin which causes a dose-dependent peripheral neuropathy in **\*\*\*vivo\*\*\*** and inhibits dorsal root ganglion (DRG) neurite outgrowth in vitro. The mechanism of suramin-induced cyto- and neurotoxicity remains unclear. Calcium is a key signal **\*\*\*transducer\*\*\*** in cellular responses to a variety of physiological and pathogenic stimuli. In the present study, we have determined the role of calcium in suramin-induced neurotoxicity in dorsal root ganglion neurons in vitro. Suramin-induced inhibition of neurite outgrowth and induction of **\*\*\*neuronal\*\*\*** cell death were dose-related phenomena. A low level of extracellular calcium significantly reduced suramin-induced inhibition of neurite outgrowth and delayed **\*\*\*neuronal\*\*\*** cell death in vitro. Nimodipine (100 microM), an L-type voltage-sensitive calcium channel (VSCC) inhibitor, mimicked low calcium medium and protected neurite outgrowth in regular calcium medium supplemented with 300 microM suramin. TMB-8 (100 microM), an inhibitor of intracellular calcium release, failed to protect neurite outgrowth against the **\*\*\*toxin\*\*\***. Calmidazolium (10 microM), a potent calmodulin inhibitor, and calpain inhibitor peptide (CIP, 10 microM) protected neurite outgrowth against suramin. The results support the hypothesis that the calcium signaling system is important in suramin-induced neurotoxicity. Influx of extracellular calcium is more important than release of intracellular calcium in causing cell injury in vitro.

L4 ANSWER 12 OF 18 MEDLINE  
 AN 96375823 MEDLINE  
 DN 96375823  
 TI Vasoactive intestinal polypeptide modulation of nicotinic ACh receptor channels in rat intracardiac neurons.  
 AU Cuevas J; Adams D J  
 CS Department of Molecular and Cellular Pharmacology, University of Miami, School of Medicine, FL 33101, USA.  
 NC HL-35422 (NHLBI)

HL-07188 (NHLBI)  
 SO JOURNAL OF PHYSIOLOGY, (1996 Jun 1) 493 (Pt 2) 503-15.  
 Journal code: JQV. ISSN: 0022-3751.  
 CY ENGLAND: United Kingdom  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199705  
 AB 1. The effects of vasoactive intestinal polypeptide (VIP) on isolated parasympathetic neurones of rat intracardiac ganglia were examined under voltage clamp using dialysed and perforated patch whole-cell and excised outside-out membrane patch recording configurations. 2. VIP reversibly potentiated nicotinic ACh-evoked whole-cell currents, with half-maximal potentiation (EC50) obtained with 260 pM VIP. However, VIP had no effect on muscarinic ACh-evoked currents, ATP-evoked currents, or depolarization-activated ionic currents in these neurones. 3. VIP-induced potentiation of nicotinic ACh-evoked whole-cell currents was observed following cell dialysis, and was inhibited reversibly by bath application of the VIP receptor-binding inhibitor L-8-K (5 microM) or the **\*\*\*neuronal\*\*\*** nicotinic receptor antagonist mecamylamine (3 microM). 4. The signal **\*\*\*transduction\*\*\*** pathway mediating VIP-induced potentiation of nicotinic ACh-evoked currents involves a guanine nucleotide-binding protein (G-protein) but not cyclic AMP. Intracellular application of 100 microM GDP-beta-S, or pre-incubation of neurones with pertussis **\*\*\*toxin\*\*\***, inhibited VIP-induced potentiation of ACh-evoked whole-cell currents. 5. In outside-out membrane patches, co-application of ACh (4 microM) and VIP (4 nM) decreased the duration of closings between bursts and clusters of bursts of ACh single-channel activity relative to control (4 microM ACh alone). VIP, however, did not alter single ACh receptor channel current amplitude, duration of closings and openings within a burst, or mean burst duration. 6. VIP-induced modification of nicotinic ACh receptor channel kinetics results in an increase in the open-channel probability which is sufficient to account for the VIP-mediated potentiation of nicotinic ACh-evoked whole-cell currents. 7. The potentiation of nicotinic ACh-evoked currents by VIP is

likely to account for the altered \*\*\*neuronal\*\*\* activity observed in the mammalian intracardiac ganglia in \*\*\*vivo\*\*\* and consequent changes in heart rate and cardiac contractility.

L4 ANSWER 13 OF 18 MEDLINE  
AN 95344784 MEDLINE  
DN 95344784  
TI Pertussis \*\*\*toxin\*\*\* specifically inhibits growth cone guidance by a mechanism independent of direct G protein inactivation.  
AU Kindt R M; Lander A D  
CS Department of Biology, Massachusetts Institute of Technology, Cambridge 02139, USA.  
SO NEURON, (1995 Jul) 15 (1) 79-88.  
Journal code: AN8: 0896-6273.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199511  
AB An assay employing patterned laminin substrata was used to screen for compounds that disrupt neurite guidance. One molecule, pertussis \*\*\*toxin\*\*\*, caused neurites to wander from patterns that normally guided them, yet had no significant effect on rates of neurite outgrowth.  
Wandering was greatest on patterns requiring frequent guidance (e.g., laminin stripes with periodic gaps). Surprisingly, the B oligomer of pertussis \*\*\*toxin\*\*\*, which lacks the subunit that inactivates G proteins, was equivalent at disrupting neurite guidance. Pertussis \*\*\*toxin\*\*\* probably acts by binding cell surface carbohydrates, since neurites lacking complex-type N-linked oligosaccharides were insensitive to the effects of the \*\*\*toxin\*\*\*. The B oligomer also blocked growth cone collapse induced by a brain membrane-derived factor, such factors are thought to act as repulsive guidance cues in \*\*\*vivo\*\*\*. That a single reagent can inhibit \*\*\*neuronal\*\*\* responses to both attractive and repulsive guidance cues suggests that such cues may share signaling pathways.

L4 ANSWER 14 OF 18 MEDLINE  
AN 95179327 MEDLINE  
DN 95179327  
TI Fast inhibition of inwardly rectifying K+ channels by multiple neurotransmitter receptors in oligodendroglia.  
AU Karschin A; Wischmeyer E; Davidson N; Lester H A  
CS Max-Planck-Institute for Biophysical Chemistry, Göttingen,

Germany.  
NC GM:29836 (NIGMS)  
SO EUROPEAN JOURNAL OF NEUROSCIENCE, (1994 Nov 1) 6 (11) 1736-64.  
Journal code: BYG: ISSN: 0953-816X.  
CY ENGLAND: United Kingdom  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199506  
AB An essential function of myelinating oligodendroglia in the mammalian central nervous system is the regulation of extracellular potassium levels by means of a prominent inwardly rectifying K+ current. Cardiac and \*\*\*neuronal\*\*\* K+ inward rectifiers are either activated by hyperpolarizing voltages or controlled by neurotransmitters through the action of receptor-activated G proteins. Neuromodulation of inward rectifiers has not previously been considered as a way to regulate oligodendrocyte function. Here we report the expression of serotonin, somatostatin and muscarinic acetylcholine G protein-coupled receptors in rat brain oligodendrocytes. Activation of these receptors leads to pertussis \*\*\*toxin\*\*\*-sensitive inhibition of inwardly rectifying K+ channels within < 1 s. By contrast, in the heart and in neurons, similar pathways activate an inwardly rectifying conductance. Thus, transmitter-mediated blockade of inward rectifiers appears to be an oligodendrocyte-specific variation of a common motif for convergent signalling pathways. In \*\*\*vivo\*\*\*, expression of this mechanism, which may be dependent on neuron-glia signalling, may have a regulatory role in K+ homeostasis during neuron activity in the central nervous system.

L4 ANSWER 15 OF 18 MEDLINE  
AN 94191900 MEDLINE  
DN 94191900  
TI In vitro labeling strategies for identifying primary neural tissue and a \*\*\*neuronal\*\*\* cell line after transplantation in the CNS.  
AU Onifer S M; White L A; Whittermore S R; Holets V R  
CS Department of Cell Biology and Anatomy, University of Miami School of Medicine, FL 33136.  
NC NS26887 (NINDS)  
NS07044:16 (NINDS)  
SO CELL TRANSPLANTATION, (1993 Mar-Apr) 2 (2) 131-49.  
Journal code: B02: ISSN: 0963-6897.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)

LA English  
FS Priority Journals  
EM 199407  
AB Potential labels for identifying embryonic raphe neurons and a clonal, neuronally differentiating, raphe-derived cell line, RN33B, in CNS transplantation studies were tested by first characterizing the labels in vitro. The labels that were tested included 4,6-diamidino-2-phenylindole hydrochloride, 1,1'-dioctadecyl-3,3',3'-tetramethylindocarbocyanine perchlorate, the Escherichia coli lacZ gene, Fast Blue, Fluoro-Gold, fluorescein-conjugated latex microspheres, fluorescein isothiocyanate-conjugated or nonconjugated Phaseolus vulgaris leucoagglutinin, methyl o-(6-amino-3'-imino-3H-xanthen-9-yl) benzoate monohydrochloride, or tetanus \*\*\*toxin\*\*\* C fragment. Subsequently, the optimal in vitro labels for embryonic raphe neurons and for RN33B cells were characterized in \*\*\*vivo\*\*\* after CNS transplantation. In vitro, 1,1'-dioctadecyl-3,3',3'-tetramethylindocarbocyanine perchlorate (DiI) optimally labeled embryonic neurons. The Escherichia coli lacZ gene optimally labeled RN33B cells. Most labels were rapidly diluted in cultures of embryonic astrocytes and proliferating RN33B cells. Some labels were toxic and were often retained in cellular debris. In \*\*\*vivo\*\*\*, DiI was visualized in transplanted, DiI-labeled raphe neurons, but not in astrocytes up to 1 mo posttransplant. DiI-labeled host cells were seen after transplantation of lysed, DiI-labeled cells. beta-Galactosidase was visualized in transplanted, Escherichia coli lacZ gene-labeled RN33B cells after 15 days in \*\*\*vivo\*\*\*. No beta-galactosidase was seen in host cells after transplantation of lysed, lacZ-labeled RN33B cells. The results demonstrate that labels for CNS transplantation studies should be optimized for the specific population of donor cells under study, with the initial step being characterization in vitro followed by in \*\*\*vivo\*\*\* analysis. Appropriate controls for false-positive labeling of host cells should always be assessed.

L4 ANSWER 16 OF 18 MEDLINE  
AN 94170397 MEDLINE  
DN 94170397  
TI Platelet-activating factor: a putative neuromodulator and mediator in the pathophysiology of brain injury.  
AU Yue T L; Feuerstein G Z  
CS Department of Cardiovascular Pharmacology, SmithKline Beecham

Pharmaceuticals, King of Prussia, PA 19406-0939.

SO CRITICAL REVIEWS IN NEUROBIOLOGY, (1994) 8 (1-2)  
11-24. Ref: 88

Journal code: CRR. ISSN: 0892-0915.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)

(REVIEW, TUTORIAL)

LA English

FS Priority Journals

EM 199406

AB Platelet-activating factor (1-O-hexadecyl-2-acetyl-sn-glycero-3-phosphocholine [PAF]) is a potent lipid autotoxin produced by many cell

types. PAF is produced by cultured rat cerebellar neurons and

human fetal

brain cells, and has been extracted from brain tissue. Multiple PAF

receptors have been demonstrated in brain tissue. PAF stimulates

intracellular  $Ca^{2+}$  mobilization and phosphatidylinositol (PI)

metabolism

in \*\*\*transformed\*\*\* \*\*neural\*\*\* cell lines via the PAF

receptor, to which both pertussis \*\*\*toxin\*\*\* (PTX)-sensitive

and

-insensitive G protein appear to couple. PAF has potent actions on

cerebral vessels and cerebral metabolism when administered in

\*\*\*vivo\*\*\*

. Direct \*\*\*neural\*\*\* effects of PAF, such as inhibition of

acetylcholine release, are observed in vitro. Excessive PAF

production in

pathological states of the nervous system, such as neurotrauma and

stroke,

has been shown. In multiple studies in rodent and non-rodent

models using

highly specific and potent PAF antagonists, reversal or prevention

of key

consequences of brain injury, such as hypoperfusion following

ischemia,

reperfusion and edema, inflammatory cell accumulation,

neurologic/motor

deficits, and \*\*\*neural\*\*\* salvage, has been demonstrated.

These

studies taken together support a role for PAF as an important

mediator in

the pathophysiology of brain injury.

L4 ANSWER 17 OF 18 MEDLINE

AN 94037127 MEDLINE

DN 94037127

TI Metabolic mapping with cellular resolution: c-fos vs.

2-deoxyglucose.

AU Sharp F R; Sagar S M; Swanson R A

CS Department of Neurology, University of California at San

Francisco..

NC NS27864 (NINDS)

NS27488 (NINDS)

SO CRITICAL REVIEWS IN NEUROBIOLOGY, (1993) 7 (3-4)

205-28. Ref: 159

Journal code: CRR. ISSN: 0892-0915.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)

(REVIEW, ACADEMIC)

LA English

FS Priority Journals

EM 199402

AB 2-Deoxyglucose (2DG) studies have been most useful in

mapping activated

regions of the nervous system. Cellular localization studies using

2DG

have been less rewarding, but results are consistent with current

views

that increases of 2DG accumulation produced by synaptic activation

represent increases in glycolytic glucose metabolism occurring

mainly in

presynaptic \*\*\*neural\*\*\* and possibly glial elements.

Immediate

early genes (IEGs), including the fos, jun, and NGFI-A families,

are

induced by a wide variety of intracellular signaling pathways. The

nuclear

localization of the protein products of these genes and their

induction by

a variety of stimuli make them useful in metabolic activation

studies

carried out at the cellular level. IEGs have been induced in neurons

by

osmotic, bacterial endotoxin, steroids, stress, and other hormonal

stimuli; by light, auditory, painful, and other sensory stimuli; during

stimulation of motor cortex and other motor behaviors, and by

various

drugs and \*\*\*toxins\*\*\* that act on a variety of neurotransmitter

systems, including dopamine and glutamate. In addition, the

localization

of c-fos gene expression identifies cells that respond to growth

factors

in \*\*\*vivo\*\*\*. Retinal Muller cells, the major glial cell type of

the

retina, demonstrate nuclear Fos immunostaining after the

intravitreal

injection of epidermal growth factor (EGF) or

\*\*\*transforming\*\*\*

growth factor-alpha (TGF-alpha). This observation demonstrates

that adult

glia can respond to these growth factors in \*\*\*vivo\*\*\*. The

investigation of early response gene expression may be particularly

useful

for elucidating the role of trophic factors in the cellular response to

central nervous system injury.

L4 ANSWER 18 OF 18 MEDLINE

AN 92343492 MEDLINE

DN 92343492

TI NMDA receptor-mediated arachidonic acid release in neurons:

role in signal

\*\*\*transduction\*\*\* and pathological aspects.

AU Lazarewicz J W; Salinska E; Wroblewski J T

CS Fidia-Georgetown Institute for the Neurosciences, Georgetown

University

School of Medicine, Washington DC

SO ADVANCES IN EXPERIMENTAL MEDICINE AND

BIOLOGY, (1992) 318 73-89.

Journal code: 2LU. ISSN: 0065-2598.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199210

AB The N-methyl-D-aspartate (NMDA)-sensitive subtype of

glutamate receptor,

which gates  $Ca^{2+}$ -permeable ion channels, is known for its role in

learning and memory formation, in the induction of long-term

potentiation,

and also in seizure activity and neurotoxicity. In primary cultures of

cerebellar neurons, agonists of NMDA receptors induce a

dose-dependent

release of  $[^3H]$ arachidonic acid ( $[^3H]AA$ ), which is potentiated by

activation of the glycine-positive modulatory site and inhibited by

NMDA

receptor antagonists. NMDA receptor-induced  $[^3H]AA$  release is

inhibited by

quinacrine and partially depends on the presence of extracellular

calcium.

The  $[^3H]AA$  release is not sensitive, however, to pretreatment with

pertussis or cholera \*\*\*toxin\*\*\*, which suggests a

$Ca^{2+}$ -dependent

activation of phospholipase A2 not employing G proteins.

Pretreatment of

cultures with the natural and semisynthetic sphingolipids GT1b and

PKS 3,

respectively, inhibits NMDA receptor-mediated  $[^3H]AA$  release.

We also

demonstrated glutamate-evoked  $[^3H]AA$  release from rat

hippocampal slices,

which is NMDA receptor mediated, calcium dependent and

sensitive to

quinacrine. Arachidonic acid and its metabolites have been shown

to play a

role as second messengers and to modulate \*\*\*neural\*\*\*

activity.

Moreover, they are thought to act as transsynaptic modulators in the

mechanism of NMDA receptor-induced long-term potentiation in

the

hippocampus. Their role in ischemic brain pathology has also been

postulated. Our experiments on cultured cerebellar granule cells,

incubated in a  $Mg^{2+}$ -free medium deprived of glucose and

oxygen,

demonstrated a time-dependent stimulation of  $[^3H]AA$  release.

This release

was inhibited by antagonists of NMDA receptors and by quinacrine.

Stimulation of NMDA-sensitive glutamate receptors and the

subsequent



calcium-mediated activation of phospholipase A2 may play a role in the in  
 \*\*\*in vivo\*\*\* release of arachidonic acid during brain ischemia.  
 This hypothesis is supported by the observation that the enhanced level of thromboxane B2 in the gerbil brain after 5 min of global ischemia is reduced by the systemic application of either the NMDA antagonist MK-801 or the ganglioside GM1.

=> d his

(FILE 'HOME' ENTERED AT 09:24:45 ON 21 SEP 2000)

FILE MEDLINE ENTERED AT 09:24:53 ON 21 SEP 2000

L1 80711 S NEURONAL/AB,BI  
 L2 5877 S L1 AND (TRANSECT? OR TRANSFORM? OR TRANSDUCT?)/AB,BI  
 L3 180 S L2 AND TOXIN#/AB,BI  
 L4 18 S L3 AND VIVO/AB,BI

=> s l3 and oncogene/ab,bi

49585 ONCOGENE/BI  
 5413360 AB/FA  
 14886 ONCOGENE/AB  
 (ONCOGENE/BI (L) AB/FA)  
 49585 ONCOGENE/BI  
 L5 9 L3 AND ONCOGENE/AB,BI

=> d 1-bib ab

YOU HAVE REQUESTED DATA FROM 9 ANSWERS -  
 CONTINUE? Y(N)?

L5 ANSWER 1 OF 9 MEDLINE  
 AN 2000312858 MEDLINE  
 DN 20312858  
 TI \*\*\*Neuronal\*\*\* apoptosis induced by pharmacological concentrations of 3-hydroxykynurenine: characterization and protection by dantrolene and Bel-2 overexpression.  
 AU Wei H; Leeds P; Chen R W; Wei W; Leng Y; Bredesen D E; Chuang D M  
 CS Section on Molecular Neurobiology, Biological Psychiatry Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland, USA.  
 SO JOURNAL OF NEUROCHEMISTRY, (2000 Jul) 75 (1) 81-90.  
 Journal code: JAV. ISSN: 0022-3042.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)

LA English  
 FS Priority Journals  
 EM 200009  
 EW 20000904  
 AB We have studied neurotoxicity induced by pharmacological concentrations of 3-hydroxykynurenine (3-HK), an endogenous \*\*\*toxin\*\*\* certain neurodegenerative diseases, in cerebellar granule cells, PCI2 pheochromocytoma cells, and GT1-7 hypothalamic neurosecretory cells. In all three cell types, the toxicity was induced in a dose-dependent manner by 3-HK at high micromolar concentrations and had features characteristic of apoptosis, including chromatin condensation and internucleosomal DNA cleavage. In cerebellar granule cells, the 3-HK neurotoxicity was unaffected by xanthine oxidase inhibitors but markedly potentiated by superoxide dismutase and its hemelike mimetic, MnTBAP [manganese(III) tetrakis(benzoic acid)porphyrin chloride]. Catalase blocked 3-HK neurotoxicity in the absence and presence of superoxide dismutase or MnTBAP. The formation of H2O2 was demonstrated in PCI2 and GT1-7 cells treated with 3-HK, by measuring the increase in the fluorescent 2,7-dichlorofluorescein. In both PCI2 and cerebellar granule cells, inhibitors of the neutral amino acid transporter that mediates the uptake of 3-HK failed to block 3-HK toxicity. However, their toxicity was slightly potentiated by the iron chelator, deferoxamine. Taken together, our results suggest that neurotoxicity induced by pharmacological concentrations of 3-HK in these cell types is mediated primarily by H2O2, which is formed most likely by auto-oxidation of 3-HK in extracellular compartments. 3-HK-induced death of PCI2 and GT1-7 cells was protected by dantrolene, an inhibitor of calcium release from the endoplasmic reticulum. The protection by dantrolene was associated with a marked increase in the protein level of Bel-2, a prominent antiapoptotic gene product. Moreover, overexpression of Bel-2 in GT1-7 cells elicited by gene \*\*\*transfection\*\*\* suppressed 3-HK toxicity. Thus, dantrolene may elicit its neuroprotective effects by mechanisms involving up-regulation of the level and function of Bel-2 protein.

L5 ANSWER 2 OF 9 MEDLINE  
 AN 1999402800 MEDLINE

DN 99402800  
 TI Neurite extension occurs in the absence of regulated exocytosis in PCI2 subclones.  
 AU Leoni C; Menegon A; Benfenati F; Toniolo D; Pennuto M; Valtorta F  
 CS San Raffaele Scientific Institute, Consiglio Nazionale delle Ricerche Center for Cellular and Molecular Pharmacology and B. Cecarelli Center for Neurobiology, University of Milan, Milan, Italy.  
 SO MOLECULAR BIOLOGY OF THE CELL, (1999 Sep) 10 (9) 2919-31.  
 Journal code: BAU. ISSN: 1059-1524.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199912  
 AB We have investigated the process leading to differentiation of PCI2 cells.

This process is known to include extension of neurites and changes in the expression of subsets of proteins involved in cytoskeletal rearrangements or in neurosecretion. To this aim, we have studied a PCI2 clone (trk-PCI2) stably \*\*\*transfected\*\*\* with the nerve growth factor receptor TrkA. These cells are able to undergo both spontaneous and neurotrophin-induced morphological differentiation. However, both undifferentiated and nerve growth factor-differentiated trk-PCI2 cells appear to be completely defective in the expression of proteins of the secretory apparatus, including proteins of synaptic vesicles and large dense-core granules, neurotransmitter transporters, and neurotransmitter-synthesizing enzymes. These results indicate that neurite extension can occur independently of the presence of the neurosecretory machinery, including the proteins that constitute the fusion machine, suggesting the existence of differential activation pathways for the two processes during \*\*\*neuronal\*\*\* differentiation. These findings have been confirmed in independent clones obtained from PCI2-27, a previously characterized PCI2 variant clone globally incompetent for regulated secretion. In contrast, the integrity of the Rab cycle appears to be necessary for neurite extension, because antisense oligonucleotides against the neurospecific isoform of Rab-guanosine diphosphate-dissociation inhibitor significantly interfere

with process formation.

LS ANSWER 3 OF 9 MEDLINE  
AN 1999253888 MEDLINE  
DN 99253888  
TI GDNF: a novel factor with therapeutic potential for neurodegenerative disorders.  
AU Walton K M  
CS Department of Neurobiology, Cephalon, Inc., West Chester, PA 19380, USA.  
SO MOLECULAR NEUROBIOLOGY, (1999 Feb) 19 (1) 43-59.  
Journal code: AH6. ISSN: 0893-7648.

CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199908

AB The identification of novel factors that promote survival could have profound effects on developing new therapeutics for neurodegenerative disorders. Glial cell line-derived neurotrophic factor (GDNF) is a novel protein purified and cloned based on its marked ability to promote dopaminergic \*\*\*neural\*\*\* function. GDNF, now known to be the first identified member of a family of factors, signals through previously known receptor tyrosine kinase, Ret. Unlike most ligands for receptor tyrosine kinases, GDNF does not bind and activate Ret directly, but requires the presence of GPI-linked coreceptors. There are several coreceptors with differing affinities for the GDNF family members. The

profile of coreceptors in a cell may determine which factor preferentially activates Ret. In vivo differences in localization of the GDNF family members, its coreceptors and Ret suggest this ligand/receptor interaction has extensive and multiple functions in the CNS as well as in peripheral tissues. GDNF promotes survival of several \*\*\*neural\*\*\* populations both in vitro and in vivo. Dopaminergic \*\*\*neural\*\*\* survival and function are preserved by GDNF in vivo when challenged by the \*\*\*toxins\*\*\* MPTP and 6-hydroxydopamine. Furthermore, GDNF improves the symptoms of pharmacologically induced Parkinson's disease in monkeys. Several motor neuron populations isolated in vitro are also rescued by

GDNF. In vivo, GDNF protects these neurons from programmed cell death associated with development and death induced by \*\*\*neural\*\*\* transection. These experiments suggest that GDNF may provide significant therapeutic opportunities in several neurodegenerative disorders.

LS ANSWER 4 OF 9 MEDLINE  
AN 1998389793 MEDLINE  
DN 98389793

TI mu-Opioid receptor activates signaling pathways implicated in cell survival and translational control.  
AU Polakiewicz R D, Schieffer S M, Gingras A C, Sonnenberg N, Comb M J  
CS Cell Signaling Laboratory, New England Biolabs, Beverly, Massachusetts 01915, USA.

NC DA05706 (NIDA)  
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Sep 4) 273 (36) 23534-41.  
Journal code: HIV. ISSN: 0021-9258.

CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals; Cancer Journals  
EM 199812

AB The mu-opioid receptor mediates the analgesic and addictive properties of morphine. Despite the clinical importance of this receptor and many years of pharmacological research, few G-protein-coupled receptor and signaling mechanisms triggered by morphine and other mu-opioid agonists have been described. We report that mu-opioid agonists stimulate three different effectors of a phosphoinositide 3-kinase (PI3K)-dependent signaling cascade. By using a cell line stably \*\*\*transfected\*\*\* with the mu-opioid receptor cDNA, we show that the specific agonist [D-Ala2,N-Me-Phe4,Gly5-o]enkephalin (DAMGO) stimulates the activity of Akt, a serine/threonine protein kinase implicated in protecting neurons from apoptosis. Activation of Akt by DAMGO correlates with its phosphorylation at serine-473. The selective PI3K inhibitors wortmannin and LY294002 blocked phosphorylation of this site, previously shown to be necessary for Akt enzymatic activity. DAMGO also stimulates the phosphorylation of two other downstream effectors of PI3K, the p70 S6 kinase and the repressors of mRNA translation, 4E-BP1 and 4E-BP2. Upon mu-opioid receptor stimulation, p70 S6 kinase is activated and

phosphorylated at threonine 389 and at threonine 421/serine 424. Phosphorylation of p70 S6 kinase and 4E-BP1 is also repressed by PI3K inhibitors as well as by rapamycin, the selective inhibitor of FRAP/mTOR.

Consistent with these findings, DAMGO-stimulated phosphorylation of 4E-BP1

impairs its ability to bind the translation initiation factor eIF-4E. These results demonstrate that the mu-opioid receptor activates signaling pathways associated with \*\*\*neural\*\*\* survival and translational control, two processes implicated in \*\*\*neural\*\*\* synaptic plasticity.

LS ANSWER 5 OF 9 MEDLINE  
AN 1998355475 MEDLINE  
DN 98355475

TI Complement C5a anaphylatoxin fragment causes apoptosis in TGW neuroblastoma cells.

AU Farkas I, Baranyi L, Liposits Z S, Yamamoto T, Okada H  
CS Department of Molecular Biology, Nagoya City University School of Medicine, Nagoya, Japan.  
SO NEUROSCIENCE, (1998 Oct) 86 (3) 903-11.  
Journal code: NZR. ISSN: 0306-4522.

CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199901

EW 19990104  
AB Human neuroblastoma TGW cells express a C5a anaphylatoxin receptor-like molecule termed \*\*\*neural\*\*\* C5a receptor. A C5a-receptor fragment peptide (termed PR226-multiple antigenic peptide) can induce rapid apoptosis in TGW cells via \*\*\*neural\*\*\* C5a receptor-associated signal \*\*\*transduction\*\*\* pathways. In order to analyse role of activated complement system in neurodegeneration, TGW cells were exposed to an oligomer form of a C5a fragment (amino acids: 37-53) peptide termed PL37-multiple antigenic peptide. Upon treatment with PL37-multiple antigenic peptide, an increased nuclear c-fos expression was shown within 30 min. DNA fragmentation, a hallmark of apoptosis, was noted within 4 h. Extracellular administration of 100 nM PL37-multiple antigenic peptide evoked inward calcium current pulses. At higher doses (0.5 microM-1

microM), PL37-multiple antigenic peptide evoked higher current pulses, followed by an irreversible, high inward current. To exert its apoptotic effect, PL37-multiple antigenic peptide utilizes a pertussis \*\*\*toxin\*\*\* -sensitive signal \*\*\*transduction\*\*\* pathway associated with the \*\*\*neural\*\*\* C5a receptor. Activation of the complement system and therefore release of C5a has already been reported in Alzheimer's disease. In addition, the presence of the Kunitz-type proteinase inhibitors indicates an impaired protease function and a possible abnormal fragmentation of C5a anaphylatoxin. Our data suggest that neurons expressing \*\*\*neural\*\*\* C5a receptor are more vulnerable to the apoptosis associated with the \*\*\*neural\*\*\* C5a receptor and the possibility that abnormal activation of C5a receptor and C5a anaphylatoxin fragments might be involved in the pathogenesis of Alzheimer's disease.

L5 ANSWER 6 OF 9 MEDLINE  
AN 1998177184 MEDLINE  
DN 98177184  
TI A \*\*\*neural\*\*\* C5a receptor and an associated apoptotic signal  
\*\*\*transduction\*\*\* pathway.  
AU Farkas I; Baranyi L; Takahashi M; Fukuda A; Liposits Z; Yamamoto T; Okada H  
CS Department of Molecular Biology, Nagoya City University School of Medicine, Nagoya 467, Japan.  
SO JOURNAL OF PHYSIOLOGY, (1998 Mar 15) 507 (Pt 3) 679-87  
Journal code: JQV. ISSN: 0022-3751.  
CY ENGLAND: United Kingdom  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199807  
AB 1. We report the first experimental evidence of a \*\*\*neural\*\*\* C5a receptor (nC5aR) in human cells of \*\*\*neural\*\*\* origin. Expression of nC5aR mRNA was demonstrated by the reverse transcriptase-polymerase chain reaction (RT-PCR) in TGW human neuroblastoma cells. 2. Expression of a functional C5aR was supported by the finding that C5a evoked a transient increase in the intracellular calcium level as measured by flow cytometry (FACS). 3. To analyse the function of the nC5aR, an antisense

peptide fragment of the C5aR was used. Previous data showed that a C5aR fragment (a peptide termed PR226) has C5aR agonist and antagonist effects in U-937 cells depending on the concentration of the peptide. We found that a multiple antigenic peptide (MAP) form of the same peptide (termed PR226-MAP) induced rapid elevation of nuclear c-fos immunoreactivity and resulted in DNA fragmentation, a characteristic sign of apoptosis, in TGW cells. 4. Early electrophysiological events characteristic of apoptosis were also detected: intermittent calcium current pulses were recorded within 1-2 min of peptide administration. C5a pretreatment delayed the onset of this calcium influx. 5. We also demonstrated that the apoptotic pathway is linked to nC5aR via pertussis \*\*\*toxin\*\*\* -sensitive G-proteins. 6. Although the function of C5a and its receptor on neurons is unknown, these results suggest that an abnormal activation of this signal \*\*\*transduction\*\*\* pathway can result in apoptosis and, subsequently, in neurodegeneration.

L5 ANSWER 7 OF 9 MEDLINE  
AN 94037127 MEDLINE  
DN 94037127  
TI Metabolic mapping with cellular resolution: c-fos vs. 2-deoxyglucose.  
AU Sharp F R; Sagar S M; Swanson R A  
CS Department of Neurology, University of California at San Francisco.  
NC NS27864 (NINDS)  
NS27488 (NINDS)  
SO CRITICAL REVIEWS IN NEUROBIOLOGY, (1993) 7 (3-4) 205-28. Ref: 159  
Journal code: CRR. ISSN: 0892-0915.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, ACADEMIC)  
LA English  
FS Priority Journals  
EM 199402  
AB 2-Deoxyglucose (2DG) studies have been most useful in mapping activated regions of the nervous system. Cellular localization studies using 2DG have been less rewarding, but results are consistent with current views that increases of 2DG accumulation produced by synaptic activation represent increases in glycolytic glucose metabolism occurring

mainly in presynaptic \*\*\*neural\*\*\* and possibly glial elements. Immediate early genes (IEGs), including the fos, jun, and NGFI-A families, are induced by a wide variety of intracellular signaling pathways. The nuclear localization of the protein products of these genes and their induction by a variety of stimuli make them useful in metabolic activation studies carried out at the cellular level. IEGs have been induced in neurons by osmotic, bacterial endotoxin, steroids, stress, and other hormonal stimuli; by light, auditory, painful, and other sensory stimuli; during stimulation of motor cortex and other motor behaviors; and by various drugs and \*\*\*toxins\*\*\* that act on a variety of neurotransmitter systems, including dopamine and glutamate. In addition, the localization of c-fos gene expression identifies cells that respond to growth factors in vivo. Retinal Muller cells, the major glial cell type of the retina, demonstrate nuclear Fos immunostaining after the intravitreal injection of epidermal growth factor (EGF) or \*\*\*transforming\*\*\* growth factor-alpha (TGF-alpha). This observation demonstrates that adult glia can respond to these growth factors in vivo. The investigation of response gene expression may be particularly useful for elucidating the role of trophic factors in the cellular response to central nervous system injury.  
L5 ANSWER 8 OF 9 MEDLINE  
AN 90150622 MEDLINE  
DN 90150622  
TI Small molecular weight GTP-binding proteins and signal \*\*\*transduction\*\*\*.  
AU Yamamoto K; Tanimoto T; Kim S; Kikuchi A; Takai Y  
CS Department of Biochemistry, Kobe University School of Medicine, Japan.  
SO CLINICA CHIMICA ACTA, (1989 Dec 15) 185 (3) 347-55.  
Journal code: DCC. ISSN: 0009-8981.  
CY Netherlands  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199005  
AB We have separated multiple GTP-binding proteins (G proteins) having Mr values of about 20,000 (small Mr G proteins) from bovine brain membranes, purified to near homogeneity and characterized two novel G proteins

designated as smg p25A and smg p21, the c-Ki-ras protein (c-Ki-ras p21) and the two rho proteins (rho p20 and rho p21). smg p25A is present abundantly in brain and adrenal medulla. This G protein is also found in rat pheochromocytoma PC-12 cells, and its mRNA level increased after differentiation of the cells into neuron-like cells in response to nerve growth factor or dibutyryl cyclic AMP. These results suggest that smg p25A plays an important role in the regulation of \*\*\*neural\*\*\* functions. In contrast, smg p21 is found in most tissues. This G protein has the same putative effector domain as ras p21s, suggesting that smg p21 exerts the actions similar and/or antagonistic to those of ras p21s. In fact, smg p21 has been found to be identical with the protein encoded by the Krev-1 gene recently isolated as a gene suppressing the \*\*\*transforming\*\*\* action of Ki-ras p21 in NIH/3T3 cells. On the other hand, rho p20 and rho p21 are ADP-ribosylated by an ADP-ribosyltransferase contained or contaminated in botulinum \*\*\*toxin\*\*\* type C1, presumably C3. Botulinum ADP-ribosyltransferase C3 has recently been shown to induce morphological changes similar to those induced by ras p21 in fibroblasts. Thus, small Mr G proteins are part of a huge network of intracellular regulatory systems and play important roles in the regulation of various cell functions including cell \*\*\*transformation\*\*\*, proliferation and differentiation.

L5 ANSWER 9 OF 9 MEDLINE  
AN 90040817 MEDLINE  
DN 90040817  
T1 Differentiation of PC12 cells with v-src: comparison with nerve growth factor.  
AU Rausch D M; Dickens G; Doll S; Fujita K; Koizumi S; Rudkin B B; Tocco M; Eiden L E; Guroff G  
CS Unit on Molecular and Cellular Neurobiology, National Institute of Mental Health, Bethesda, MD 20892  
SO JOURNAL OF NEUROSCIENCE RESEARCH, (1989 Sep) 24 (1) 49-58.  
Journal code: KAC. ISSN: 0360-4012.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English

FS Priority Journals  
EM 199002  
AB The PC12 rat pheochromocytoma cell line is used extensively as a model to study \*\*\*neural\*\*\* differentiation. These cells resemble adrenal chromaffin cells, differentiating both morphologically and biochemically when cultured in the presence of dexamethasone, but develop a sympathetic neuron-like phenotype when cultured in the presence of nerve growth factor. Expression of the protein product of the v-src \*\*\*oncogene\*\*\* in PC12 cells also induces neurite outgrowth similar to that resulting from nerve growth factor treatment (Alemia et al: Nature 316:557-559, 1985). It is thus possible that c-src or a src-like tyrosine kinase participates in the signal \*\*\*transduction\*\*\* pathway by which nerve growth factor acts on PC12 cells. In this study a temperature-sensitive v-src gene has been introduced into PC12 cells. When cultures of these src- \*\*\*transformed\*\*\* cells are switched from the nonpermissive (40 degrees C) to the permissive (37 degrees C) temperature they elaborate neurites. The differentiation induced by src has been compared with that induced by nerve growth factor by determining whether src- \*\*\*transformed\*\*\* PC12 cells at 37 degrees C exhibit the same biochemical alterations as those induced in PC12 cells treated with nerve growth factor. Neurite extension at 37 degrees C in v-src- \*\*\*transformed\*\*\* cells, like NGF-induced differentiation, is accompanied by an increase in the nerve growth factor-inducible large external (NILE) protein. However, neurite extension in v-src- \*\*\*transformed\*\*\* cells is not blocked by the protein kinase inhibitor K-252a, which completely blocks NGF-induced neurite extension. Likewise, EGF receptor down-regulation and the development of saxitoxin and tetanus \*\*\*toxin\*\*\* binding sites are either much reduced or completely absent in src-differentiated compared with NGF-differentiated PC12 cells.  
=> d his

(FILE 'HOME' ENTERED AT 09:24:45 ON 21 SEP 2000)

FILE 'MEDLINE' ENTERED AT 09:24:53 ON 21 SEP 2000

L1 80711 S NEURONAL/AB,BI  
L2 5827 S L1 AND (TRANSFECT? OR TRANSFORM? OR TRANSDUC?)/AB,BI  
L3 180 S L2 AND TOXIN#/AB,BI  
L4 18 S L3 AND VIVO/AB,BI  
L5 9 S L3 AND ONCOGENE/AB,BI  
=> s l5 and vivo/ab,bi  
267353 VIVO/BI  
5413360 AB/FA  
230827 VIVO/AB  
(VIVO/BI (L) AB/FA)  
267353 VIVO/BI  
L6 2 L5 AND VIVO/AB,BI  
=> d l- bib ab

YOU HAVE REQUESTED DATA FROM 2 ANSWERS -  
CONTINUE? Y(N);y

L6 ANSWER 1 OF 2 MEDLINE  
AN 1999253888 MEDLINE  
DN 99253888  
T1 GDNF: a novel factor with therapeutic potential for neurodegenerative disorders.  
AU Walton K M  
CS Department of Neurobiology, Cephalon, Inc., West Chester, PA 19380, USA.  
SO MOLECULAR NEUROBIOLOGY, (1999 Feb) 19 (1) 43-59.  
Journal code: AH6. ISSN: 0893-7648.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199908  
AB The identification of novel factors that promote \*\*\*neural\*\*\* survival could have profound effects on developing new therapeutics for neurodegenerative disorders. Glial cell line-derived neurotrophic factor (GDNF) is a novel protein purified and cloned based on its marked ability to promote dopaminergic \*\*\*neural\*\*\* function. GDNF, now known to be the first identified member of a family of factors, signals through the previously known receptor tyrosine kinase, Ret. Unlike most ligands for receptor tyrosine kinases, GDNF does not bind and activate Ret directly, but requires the presence of GPI-linked coreceptors. There are several coreceptors with differing affinities for the GDNF family members.

The profile of coreceptors in a cell may determine which factor preferentially activates Ret. In \*\*\*vivo\*\*\* differences in localization of the GDNF family members, its coreceptors and Ret suggest this ligand/receptor interaction has extensive and multiple functions in the CNS as well as in peripheral tissues. GDNF promotes survival of several \*\*\*neuronal\*\*\* populations both in vitro and in \*\*\*vivo\*\*\*. Dopaminergic \*\*\*neuronal\*\*\* survival and function are preserved by GDNF in \*\*\*vivo\*\*\* when challenged by the \*\*\*toxins\*\*\* MPTP and 6-hydroxydopamine. Furthermore, GDNF improves the symptoms of pharmacologically induced Parkinson's disease in monkeys. Several neuron populations isolated in vitro are also rescued by GDNF. In \*\*\*vivo\*\*\*, GDNF protects these neurons from programmed cell death associated with development and death induced by \*\*\*neuronal\*\*\* transfection. These experiments suggest that GDNF may provide therapeutic opportunities in several neurodegenerative disorders.

L6 ANSWER 2 OF 2 MEDLINE  
 AN 94037127 MEDLINE  
 DN 94037127  
 TT Metabolic mapping with cellular resolution: c-fos vs. 2-deoxyglucose.  
 AU Sharp F R; Sagar S M; Swanson R A  
 CS Department of Neurology, University of California at San Francisco.  
 NC NS27488 (NINDS)  
 SO CRITICAL REVIEWS IN NEUROBIOLOGY, (1993) 7 (3-4) 205-28. Ref: 159  
 Journal code: CRR. ISSN: 0892-0915.  
 C.Y. United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW, ACADEMIC)  
 LA English  
 FS Priority Journals  
 EM 199402  
 AB 2-Deoxyglucose (2DG) studies have been most useful in mapping activated regions of the nervous system. Cellular localization studies using 2DG have been less rewarding, but results are consistent with current views that increases of 2DG accumulation produced by synaptic activation represent increases in glycolytic glucose metabolism occurring mainly in

presynaptic \*\*\*neuronal\*\*\* and possibly glial elements. Immediate early genes (IEGs), including the fos, jun, and NGF1-A families, are induced by a wide variety of intracellular signaling pathways. The nuclear localization of the protein products of these genes and their induction by a variety of stimuli make them useful in metabolic activation studies carried out at the cellular level. IEGs have been induced in neurons by osmotic, bacterial endotoxin, steroids, stress, and other hormonal stimuli; by light, auditory, painful, and other sensory stimuli; during stimulation of motor cortex and other motor behaviors; and by various drugs and \*\*\*toxins\*\*\* that act on a variety of neurotransmitter systems, including dopamine and glutamate. In addition, the localization of c-fos gene expression identifies cells that respond to growth factors in \*\*\*vivo\*\*\*. Retinal Muller cells, the major glial cell type of the retina, demonstrate nuclear Fos immunostaining after the intravitreal injection of epidermal growth factor (EGF) or \*\*\*transforming\*\*\* growth factor-alpha (TGF-alpha). This observation demonstrates that adult glia can respond to these growth factors in \*\*\*vivo\*\*\*. The investigation of early response gene expression may be particularly useful for elucidating the role of trophic factors in the cellular response to central nervous system injury.

=> s l3 and tumorigenic and vivo/ab,bi

5288 TUMORIGENIC  
 267353 VIVO/BI  
 5413360 AB/FA  
 230827 VIVO/AB  
 (VIVO/BI (L) AB/FA)  
 267353 VIVO/BI  
 L7 0 L3 AND TUMORIGENIC AND VIVO/AB,BI

=> s l3 and tumorigenic/ab,bi

5288 TUMORIGENIC/BI  
 5413360 AB/FA  
 4972 TUMORIGENIC/AB  
 (TUMORIGENIC/BI (L) AB/FA)  
 5288 TUMORIGENIC/BI  
 L8 0 L3 AND TUMORIGENIC/AB,BI

=> s l3 and immortaliz/ab,bi

5479 IMMORTALIZ/BI  
 5413360 AB/FA  
 5078 IMMORTALIZ/AB  
 (IMMORTALIZ/BI (L) AB/FA)  
 5479 IMMORTALIZ/BI  
 L9 2 L3 AND IMMORTALIZ/AB,BI  
 => d l- bib ab

YOU HAVE REQUESTED DATA FROM 2 ANSWERS -  
 CONTINUE? Y(N)?y

L9 ANSWER 1 OF 2 MEDLINE  
 AN 1999427870 MEDLINE  
 DN 99427870  
 TT Bradykinin receptor localization and cell signaling pathways used by bradykinin in the regulation of gonadotropin-releasing hormone secretion.  
 AU Shi B; Bhat G; Maresh V B; Brotto M; Nosek T M; Brann D W  
 CS Department of Physiology and Endocrinology, Medical College of Georgia,  
 Augusta 30912, USA.  
 NC HD-28964 (NICHHD)  
 SO ENDOCRINOLOGY, (1999 Oct) 140 (10) 4669-76.  
 Journal code: EGZ. ISSN: 0013-7227.  
 C.Y. United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals  
 EM 199912  
 EW 19991203  
 AB In a previous publication we provided evidence of a novel \*\*\*neuronal\*\*\* pathway for the control of GnRH secretion by bradykinin. The action of bradykinin appeared to be exerted through the bradykinin B2 receptor. In this study we demonstrated that the bradykinin B2 receptor is densely localized in the arcuate nucleus, median eminence, organum vasculosum of the lamina terminalis, and preoptic area, regions known to be critical for the control of GnRH secretion. To determine the mechanism of action of bradykinin in stimulating GnRH release, we used GnRH (GT1-7) cells in vitro. Bradykinin stimulation of GnRH secretion from GT1-7 cells appears to involve activation of the phospholipase C signaling pathway and mobilization of extracellular and intracellular calcium stores. Evidence to support this contention was derived from the observations that incubation of the phospholipase C inhibitor,

U-73122

with bradykinin, blocked the ability of bradykinin to stimulate release from GT1-7 cells. This effect was specific, as a nitric oxide synthase inhibitor and a cyclooxygenase inhibitor were found to have no effect on bradykinin-induced GnRH secretion, suggesting that nitric oxide and PGs do not mediate bradykinin effects. Pertussis \*\*\*toxin\*\*\* also had no effect on bradykinin action. This suggests that the bradykinin B2 receptor may be coupled to a pertussis \*\*\*toxin\*\*\* -insensitive G protein in GT1-7 cells. With respect to calcium involvement in bradykinin action, fura-2 calcium indicator studies revealed that bradykinin can rapidly increase intracellular Ca2+ levels in GT1-7 cells. A role for intracellular Ca2+ in bradykinin action was further suggested by the finding that an intracellular calcium chelator, 1,2-bis(O-aminophenoxy)ethane-N,N',N'-tetraacetic acid significantly attenuated the effects of bradykinin on GnRH release. The elevation of intracellular calcium by bradykinin appears to be due to mobilization of calcium from the endoplasmic reticulum, as incubation of the Ca2+-adenosine triphosphatase inhibitor thapsigargin, which depletes endoplasmic reticulum Ca2+ stores, significantly attenuated bradykinin action on GnRH release. Extracellular calcium may also be involved in bradykinin action, as the L-type Ca2+ channel blockers verapamil and nifedipine had no effect on bradykinin-induced GnRH release, whereas the nonselective Ca2+ channel blocker, nickel chloride, attenuated bradykinin-induced GnRH release. Taken as a whole, these studies demonstrate that the bradykinin B2 receptor is densely localized in key hypothalamic nuclei responsible for regulation of GnRH release, and that the mechanism of bradykinin stimulation of GnRH secretion involves activation of the phospholipase C signaling pathway, with a critical role implicated for calcium in bradykinin action in GT1-7 cells.

L9 ANSWER 2 OF 2 MEDLINE  
AN 1998378489 MEDLINE  
DN 98378489  
TI Nicotinic receptor-induced apoptotic cell death of hippocampal progenitor cells.  
AU Berger F; Gage F H; Vijayaraghavan S

CS Laboratory of Genetics, The Salk Institute, La Jolla, California 92037, USA.

SO JOURNAL OF NEUROSCIENCE, (1998 Sep 1) 18 (17)

6871-81.

Journal code: JDF ISSN: 0270-6474.

CY United States

DT Journal Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199811

EW 19981102

AB Nicotine has many effects on CNS functions, presumably through its action on \*\*\*neuronal\*\*\* nicotinic acetylcholine receptors (AChRs).

One subclass of AChRs that binds the snake venom \*\*\*toxin\*\*\* alpha-bungarotoxin (alpha-Bgt-AChRs) has been shown to modulate neurotransmission in the brain. We now show that alpha-Bgt-AChR activation by low doses of nicotine results in apoptotic cell death of both primary and \*\*\*immortalized\*\*\* hippocampal progenitor cells. In HC2S2, \*\*\*immortalized\*\*\* hippocampal progenitors, nicotine is cytotoxic to undifferentiated cells, whereas it spares the same cells once differentiation has been induced. The activation of alpha-Bgt-AChRs by nicotine results in the induction of the tumor suppressor protein p53 and the cdk inhibitor p21. The cytotoxic effect of nicotine is dependent on extracellular calcium levels and is probably attributable to the poor ability of undifferentiated progenitors to buffer calcium loads. The major calcium buffer in these cells, calbindin D28K, is present only after differentiation has been induced. Furthermore \*\*\*transfection\*\*\* of undifferentiated cells with calbindin results in dramatic protection against the cytotoxic effects of nicotine. These results show that nicotine abuse could have significant effects on the survival of progenitor populations in the developing and adult brain and also suggest an endogenous role for alpha-Bgt-AChRs in \*\*\*neuronal\*\*\* development and differentiation.

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FILE 'MEDLINE' ENTERED AT 09:24:53 ON 21 SEP 2000

L1 80711 S NEURONAL/AB,BI

L2 5827 S L1 AND (TRANSFECT? OR TRANSFORM? OR TRANSDUC?)/AB,BI

L3 180 S L2 AND TOXIN#/AB,BI

L4 18 S L3 AND VIVO/AB,BI

L5 9 S L3 AND ONCOGENE/AB,BI

L6 2 S L5 AND VIVO/AB,BI

L7 0 S L3 AND TUMORIGENIC AND VIVO/AB,BI

L8 0 S L3 AND TUMORIGENIC/AB,BI

L9 2 S L3 AND IMMORTALIZ//AB,BI

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ENTRY SESSION 8.29 8.44  
FULL ESTIMATED COST

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FILE 'EMBASE' ENTERED AT 09:29:23 ON 21 SEP 2000

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FILE 'BIOSIS' ENTERED AT 09:29:23 ON 21 SEP 2000

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FILE 'INPADOC' ENTERED AT 09:29:23 ON 21 SEP 2000

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=> s 15 or 16 or 17 or 18 or 19

2 FILES SEARCHED...

'AB' IS NOT A VALID FIELD CODE

3 FILES SEARCHED...

L10 19 L5 OR L6 OR L7 OR L8 OR L9

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L11 12 DUP REM L10 (7 DUPLICATES REMOVED)

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YOU HAVE REQUESTED DATA FROM 12 ANSWERS -  
CONTINUE? Y/(N)?

L11 ANSWER 1 OF 12 MEDLINE

AN 2000312858 MEDLINE

DN 20312858

TI \*\*\*Neuronal\*\*\* apoptosis induced by pharmacological concentrations of

3-hydroxykynurenine: characterization and protection by dantrolene

and Bel-2 overexpression.  
AU Wei H, Leeds P, Chen R W, Wei W, Leng Y, Bredesen D E;  
Chuang D M  
CS Section on Molecular Neurobiology, Biological Psychiatry  
Branch, National  
Institute of Mental Health, National Institutes of Health, Bethesda,  
Maryland, USA.  
SO JOURNAL OF NEUROCHEMISTRY, (2000 Jul) 75 (1) 81-90.  
Journal code: JAV. ISSN: 0022-3042.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 200009  
EW 20000904  
AB We have studied neurotoxicity induced by pharmacological  
concentrations of  
3-hydroxymurene (3-HK), an endogenous \*\*\*toxin\*\*\*  
implicated in  
certain neurodegenerative diseases, in cerebellar granule cells,  
PC12  
pheochromocytoma cells, and GT1-7 hypothalamic neurosecretory  
cells. In  
all three cell types, the toxicity was induced in a dose-dependent  
manner  
by 3-HK at high micromolar concentrations and had features  
characteristic  
of apoptosis, including chromatin condensation and  
internucleosomal DNA  
cleavage. In cerebellar granule cells, the 3-HK neurotoxicity was  
unaffected by xanthine oxidase inhibitors but markedly potentiated  
by  
superoxide dismutase and its hemelike mimetic, MnTBAP  
[manganese(III)  
tetrakis(benzoic acid)porphyrin chloride]. Catalase blocked 3-HK  
neurotoxicity in the absence and presence of superoxide dismutase  
or  
MnTBAP. The formation of H<sub>2</sub>O<sub>2</sub> was demonstrated in PC12  
and GT1-7 cells  
treated with 3-HK, by measuring the increase in the fluorescent  
product,  
2,7-dichlorofluorescein. In both PC12 and cerebellar granule cells,  
inhibitors of the neutral amino acid transporter that mediates the  
uptake  
of 3-HK failed to block 3-HK toxicity. However, their toxicity was  
slightly potentiated by the iron chelator, deferoxamine. Taken  
together,  
our results suggest that neurotoxicity induced by pharmacological  
concentrations of 3-HK in these cell types is mediated primarily by  
H<sub>2</sub>O<sub>2</sub>, which is formed most likely by auto-oxidation of 3-HK  
in  
extracellular compartments. 3-HK-induced death of PC12 and  
GT1-7 cells was  
protected by dantrolene, an inhibitor of calcium release from the  
endoplasmic reticulum. The protection by dantrolene was  
associated with a

marked increase in the protein level of Bel-2, a prominent  
antiapoptotic  
gene product. Moreover, overexpression of Bel-2 in GT1-7 cells  
elicited by  
gene \*\*\*transfection\*\*\* suppressed 3-HK toxicity. Thus,  
dantrolene may  
elicit its neuroprotective effects by mechanisms involving  
up-regulation  
of the level and function of Bel-2 protein.

L11 ANSWER 2 OF 12 MEDLINE DUPLICATE  
1  
AN 1999427870 MEDLINE  
DN 99427870  
TI Bradykinin receptor localization and cell signaling pathways used  
by  
bradykinin in the regulation of gonadotropin-releasing hormone  
secretion.  
AU Shi B; Bhat G; Mahesh V B; Brotto M; Nosek T M; Brann D W  
CS Department of Physiology and Endocrinology, Medical College  
of Georgia,  
Augusta 30912, USA.  
NC HD-28964 (NICHHD)  
SO ENDOCRINOLOGY, (1999 Oct) 140 (10) 4669-76.  
Journal code: ECG. ISSN: 0013-7227.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Abridged Index Medicus Journals; Priority Journals; Cancer  
Journals  
EM 199912  
EW 19991203  
AB In a previous publication we provided evidence of a novel  
\*\*\*neuronal\*\*\*  
pathway for the control of GnRH secretion by bradykinin. The  
action of  
bradykinin appeared to be exerted through the bradykinin B2  
receptor. In  
this study we demonstrated that the bradykinin B2 receptor is  
densely  
localized in the arcuate nucleus, median eminence, organum  
vasculosum of  
the lamina terminalis, and preoptic area, regions known to be  
critical for  
the control of GnRH secretion. To determine the mechanism of  
action of  
bradykinin in stimulating GnRH release, we used  
\*\*\*immortalized\*\*\*  
GnRH (GT1-7) cells in vitro. Bradykinin stimulation of GnRH  
secretion from  
GT1-7 cells appears to involve activation of the phospholipase C  
signaling  
pathway and mobilization of extracellular and intracellular calcium  
stores. Evidence to support this contention was derived from the  
observations that incubation of the phospholipase C inhibitor,  
U-73122  
with bradykinin, blocked the ability of bradykinin to stimulate

release  
from GT1-7 cells. This effect was specific, as a nitric oxide  
synthase  
inhibitor and a cyclooxygenase inhibitor were found to have no  
effect on  
bradykinin-induced GnRH secretion, suggesting that nitric oxide  
and PGs do  
not mediate bradykinin effects. Pertussis \*\*\*toxin\*\*\* also had  
no  
effect on bradykinin action. This suggests that the bradykinin B2  
receptor  
may be coupled to a pertussis \*\*\*toxin\*\*\* -insensitive G protein  
in  
GT1-7 cells. With respect to calcium involvement in bradykinin  
action,  
fura-2 calcium indicator studies revealed that bradykinin can rapidly  
increase intracellular Ca<sup>2+</sup> levels in GT1-7 cells. A role for  
intracellular Ca<sup>2+</sup> in bradykinin action was further suggested by the  
finding that an intracellular calcium chelator, 1,2-bis(O-  
aminophenoxy)ethane-N,N,N',N'-tetraacetic acid  
tetraacetoxymethyl ester,  
significantly attenuated the effects of bradykinin on GnRH release.  
The  
elevation of intracellular calcium by bradykinin appears to be due to  
mobilization of calcium from the endoplasmic reticulum, as  
incubation of  
the Ca<sup>2+</sup>-adenosine triphosphatase inhibitor thapsigargin, which  
depletes  
endoplasmic reticulum Ca<sup>2+</sup> stores, significantly attenuated  
bradykinin  
action on GnRH release. Extracellular calcium may also be  
involved in  
bradykinin action, as the L-type Ca<sup>2+</sup> channel blockers verapamil  
and  
nifedipine had no effect on bradykinin-induced GnRH release,  
whereas the  
nonselective Ca<sup>2+</sup> channel blocker, nickel chloride, attenuated  
bradykinin-induced GnRH release. Taken as a whole, these studies  
demonstrate that the bradykinin B2 receptor is densely localized in  
key  
hypothalamic nuclei responsible for regulation of GnRH release,  
and that  
the mechanism of bradykinin stimulation of GnRH secretion  
involves  
activation of the phospholipase C signaling pathway, with a critical  
role  
implicated for calcium in bradykinin action in GT1-7 cells.

L11 ANSWER 3 OF 12 MEDLINE  
AN 1999402800 MEDLINE  
DN 99402800  
TI Neurite extension occurs in the absence of regulated exocytosis in  
PC12  
subclones.  
AU Leoni C; Menegon A; Benfenati F; Toniolo D; Pennuto M;  
Valtorta F  
CS San Raffaele Scientific Institute, Consiglio Nazionale delle

Ricerca  
Center for Cellular and Molecular Pharmacology and B. Coccarelli  
Center  
for Neurobiology, University of Milan, Milan, Italy.  
SO MOLECULAR BIOLOGY OF THE CELL, (1999 Sep) 10 (9)  
2919-31.  
Journal code: BAU. ISSN: 1059-1524.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199912  
AB We have investigated the process leading to differentiation of PC12 cells.  
This process is known to include extension of neurites and changes in the expression of subsets of proteins involved in cytoskeletal rearrangements or in neurosecretion. To this aim, we have studied a PC12 clone (tk-PC12) stably \*\*\*transfected\*\*\* with the nerve growth factor receptor TrkA.  
These cells are able to undergo both spontaneous and neurotrophin-induced morphological differentiation. However, both undifferentiated and nerve growth factor-differentiated tk-PC12 cells appear to be completely defective in the expression of proteins of the secretory apparatus, including proteins of synaptic vesicles and large dense-core granules, neurotransmitter transporters, and neurotransmitter-synthesizing enzymes.  
These results indicate that neurite extension can occur independently of the presence of the neurosecretory machinery, including the proteins that constitute the fusion machine, suggesting the existence of differential activation pathways for the two processes during \*\*\*neuronal\*\*\* differentiation. These findings have been confirmed in independent clones obtained from PC12-27, a previously characterized PC12 variant clone globally incompetent for regulated secretion. In contrast, the integrity of the Rab cycle appears to be necessary for neurite extension, because antisense oligonucleotides against the neurospecific isoform of Rab-guanosine diphosphate-dissociation inhibitor significantly interfere with process formation.  
L11 ANSWER 4 OF 12 MEDLINE  
AN 1999253888 MEDLINE  
DN 99253888  
TI GDNF: a novel factor with therapeutic potential for neurodegenerative

disorders.  
AU Walton K M  
CS Department of Neurobiology, Cephalon, Inc., West Chester, PA 19380, USA.  
SO MOLECULAR NEUROBIOLOGY, (1999 Feb) 19 (1) 43-59.  
Journal code: AH6. ISSN: 0893-7648.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199908  
AB The identification of novel factors that promote \*\*\*neuronal\*\*\* survival could have profound effects on developing new therapeutics for neurodegenerative disorders. Glial cell line-derived neurotrophic factor (GDNF) is a novel protein purified and cloned based on its marked ability to promote dopaminergic \*\*\*neuronal\*\*\* function. GDNF, now known to be the first identified member of a family of factors, signals through the previously known receptor tyrosine kinase, Ret. Unlike most ligands for receptor tyrosine kinases, GDNF does not bind and activate Ret directly, but requires the presence of GPI-linked coreceptors. There are several coreceptors with differing affinities for the GDNF family members. The profile of coreceptors in a cell may determine which factor preferentially activates Ret. In \*\*\*vivo\*\*\* differences in localization of the GDNF family members, its coreceptors and Ret suggest this ligand/receptor interaction has extensive and multiple functions in the CNS as well as in peripheral tissues. GDNF promotes survival of several \*\*\*neuronal\*\*\* populations both in vitro and in \*\*\*vivo\*\*\*. Dopaminergic \*\*\*neuronal\*\*\* survival and function are preserved by GDNF in \*\*\*vivo\*\*\* when challenged by the \*\*\*toxins\*\*\* MPTP and 6-hydroxydopamine. Furthermore, GDNF improves the symptoms of pharmacologically induced Parkinson's disease in monkeys. Several neuron populations isolated in vitro are also rescued by GDNF. In \*\*\*vivo\*\*\*, GDNF protects these neurons from programmed cell death associated with development and death induced by \*\*\*neuronal\*\*\* transection. These experiments suggest that GDNF may provide significant therapeutic opportunities in several neurodegenerative disorders.

L11 ANSWER 5 OF 12 MEDLINE  
AN 1998389793 MEDLINE  
DN 98389793  
TI mu-Opioid receptor activates signaling pathways implicated in cell survival and translational control.  
AU Polakiewicz R D; Schiefel S M; Gingras A C; Sonenberg N; Comb M J  
CS Cell Signaling Laboratory, New England Biolabs, Beverly, Massachusetts 01915, USA.  
NC DA05706 (NIDA)  
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Sep 4) 273 (36) 23534-41.  
Journal code: HIV. ISSN: 0021-9258.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals; Cancer Journals  
EM 199812  
AB The mu-opioid receptor mediates the analgesic and addictive properties of morphine. Despite the clinical importance of this G-protein-coupled receptor and many years of pharmacological research, few intracellular signaling mechanisms triggered by morphine and other mu-opioid agonists have been described. We report that mu-opioid agonists stimulate three different effectors of a phosphoinositide 3-kinase (PI3K)-dependent signaling cascade. By using a cell line stably \*\*\*transfected\*\*\* with the mu-opioid receptor cDNA, we show that the specific agonist [D-Ala2,N-Me-Phe4,Gly5-ol]enkephalin (DAMGO) stimulates the activity of Akt, a serine/threonine protein kinase implicated in protecting neurons from apoptosis. Activation of Akt by DAMGO correlates with its phosphorylation at serine 473. The selective PI3K inhibitors wortmannin and LY294002 blocked phosphorylation of this site, previously shown to be necessary for Akt enzymatic activity. DAMGO also stimulates the phosphorylation of two other downstream effectors of PI3K, the p70 S6 kinase and the repressors of mRNA translation, 4E-BP1 and 4E-BP2. Upon mu-opioid receptor stimulation, p70 S6 kinase is activated and phosphorylated at threonine 389 and at threonine 421/serine 424. Phosphorylation of p70 S6 kinase and 4E-BP1 is also repressed by PI3K inhibitors as well as by rapamycin, the selective inhibitor of FRAP/mTOR. Consistent with these findings, DAMGO-stimulated phosphorylation of 4E-BP1



impairs its ability to bind the translation initiation factor eIF-4E. These results demonstrate that the mu-opioid receptor activates signaling pathways associated with \*\*\*neuronal\*\*\* survival and translational control, two processes implicated in \*\*\*neuronal\*\*\* development and synaptic plasticity.

L11 ANSWER 6 OF 12 MEDLINE DUPLICATE  
 2  
 AN 1998378489 MEDLINE  
 DN 98378489  
 TI Nicotinic receptor-induced apoptotic cell death of hippocampal progenitor cells.  
 AU Berger F, Gage F H, Vijayaraghavan S  
 CS Laboratory of Genetics, The Salk Institute, La Jolla, California 92037, USA  
 SO JOURNAL OF NEUROSCIENCE, (1998 Sep 1) 18 (17) 6871-81.  
 Journal code: JDF. ISSN: 0270-6474.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199811  
 EW 19981102  
 AB Nicotine has many effects on CNS functions, presumably through its action on \*\*\*neuronal\*\*\* nicotinic acetylcholine receptors (AChRs). One subclass of AChRs that binds the snake venom \*\*\*toxin\*\*\* alpha-bungarotoxin (alpha-Bgt-AChRs) has been shown to modulate neurotransmission in the brain. We now show that alpha-Bgt-AChR activation by low doses of nicotine results in apoptotic cell death of both primary and \*\*\*immortalized\*\*\* hippocampal progenitor cells. In HC2S2, \*\*\*immortalized\*\*\* hippocampal progenitors, nicotine is cytotoxic to undifferentiated cells, whereas it spares the same cells once differentiation has been induced. The activation of alpha-Bgt-AChRs by nicotine results in the induction of the tumor suppressor protein p53 and the cdk inhibitor p21. The cytotoxic effect of nicotine is dependent on extracellular calcium levels and is probably attributable to the poor ability of undifferentiated progenitors to buffer calcium loads. The major calcium buffer in these cells, calbindin D28K, is present only after differentiation has been induced. Furthermore \*\*\*transfection\*\*\* of

undifferentiated cells with calbindin results in dramatic protection against the cytotoxic effects of nicotine. These results show that nicotine abuse could have significant effects on the survival of progenitor populations in the developing and adult brain and also suggest an endogenous role for alpha-Bgt-AChRs in \*\*\*neuronal\*\*\* development and differentiation.

L11 ANSWER 7 OF 12 MEDLINE  
 AN 1998355475 MEDLINE  
 DN 98355475  
 TI Complement C3a anaphylatoxin fragment causes apoptosis in TGW neuroblastoma cells.  
 AU Farkas I, Baranyi L, Liposits Z S, Yamamoto T, Okada H  
 CS Department of Molecular Biology, Nagoya City University School of Medicine, Nagoya, Japan.  
 SO NEUROSCIENCE, (1998 Oct) 86 (3) 903-11.  
 Journal code: NZR. ISSN: 0306-4522.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199901  
 EW 19990104  
 AB Human neuroblastoma TGW cells express a C3a anaphylatoxin receptor-like molecule termed \*\*\*neuronal\*\*\* C3a receptor. A C3a-receptor fragment peptide (termed PR226-multiple antigenic peptide) can induce rapid apoptosis in TGW cells via \*\*\*neuronal\*\*\* C3a receptor-associated signal \*\*\*transduction\*\*\* pathways. In order to analyse role of activated complement system in neurodegeneration, TGW cells were exposed to an oligomer form of a C3a fragment (amino acids: 37-53) peptide termed PL37-multiple antigenic peptide. Upon treatment with PL37-multiple antigenic peptide, an increased nuclear c-fos expression was shown within 30 min. DNA fragmentation, a hallmark of apoptosis, was noted within 4 h. Extracellular administration of 100 nM PL37-multiple antigenic peptide evoked inward calcium current pulses. At higher doses (0.5 microM-1 microM), PL37-multiple antigenic peptide evoked higher current pulses, followed by an irreversible, high inward current. To exert its apoptotic effect, PL37-multiple antigenic peptide utilizes a pertussis \*\*\*toxin\*\*\* -sensitive signal \*\*\*transduction\*\*\* pathway associated with

the \*\*\*neuronal\*\*\* C3a receptor. Activation of the complement system and therefore release of C3a has already been reported in Alzheimer's disease. In addition, the presence of the Kunitz-type proteinase inhibitors indicates an impaired protease function and a possible abnormal fragmentation of C3a anaphylatoxin. Our data suggest that neurons expressing \*\*\*neuronal\*\*\* C3a receptor are more vulnerable to the apoptosis associated with the \*\*\*neuronal\*\*\* C3a receptor and the possibility that abnormal activation of C3a receptor and C3a anaphylatoxin fragments might be involved in the pathogenesis of Alzheimer's disease.

L11 ANSWER 8 OF 12 MEDLINE  
 AN 1998177184 MEDLINE  
 DN 98177184  
 TI A \*\*\*neuronal\*\*\* C3a receptor and an associated apoptotic signal \*\*\*transduction\*\*\* pathway.  
 AU Farkas I, Baranyi L, Takahashi M, Fukuda A, Liposits Z, Yamamoto T, Okada H  
 CS Department of Molecular Biology, Nagoya City University School of Medicine, Nagoya 467, Japan.  
 SO JOURNAL OF PHYSIOLOGY, (1998 Mar 15) 507 (Pt 3) 679-87.  
 Journal code: JQV. ISSN: 0022-3751.  
 CY ENGLAND; United Kingdom  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199807  
 AB 1. We report the first experimental evidence of a \*\*\*neuronal\*\*\* C3a receptor (nC3aR) in human cells of \*\*\*neuronal\*\*\* origin. Expression of nC3aR mRNA was demonstrated by the reverse transcriptase-polymerase chain reaction (RT-PCR) in TGW human neuroblastoma cells. 2. Expression of a functional C3aR was supported by the finding that C3a evoked a transient increase in the intracellular calcium level as measured by flow cytometry (FACS). 3. To analyse the function of the nC3aR, an antisense peptide fragment of the C3aR was used. Previous data showed that a C3aR fragment (a peptide termed PR226) has C3aR agonist and antagonist effects in U-937 cells depending on the concentration of the peptide. We found that

multiple antigenic peptide (MAP) form of the same peptide (termed PR226-MAP) induced rapid elevation of nuclear c-fos immunoreactivity and resulted in DNA fragmentation, a characteristic sign of apoptosis, in TGW cells. 4. Early electrophysiological events characteristic of apoptosis were also detected: intermittent calcium current pulses were recorded within 1-2 min of peptide administration. C5a pretreatment delayed the onset of this calcium influx. 5. We also demonstrated that the apoptotic pathway is linked to nC5aR via pertussis \*\*\*toxin\*\*\* -sensitive G-proteins. 6. Although the function of C5a and its receptor on neurons is unknown, these results suggest that an abnormal activation of this signal \*\*\*transduction\*\*\* pathway can result in apoptosis and, subsequently, in neurodegeneration.

L11 ANSWER 9 OF 12 EMBASE COPYRIGHT 2000 ELSEVIER

SCI: B.V.  
AN 9627097 EMBASE  
DN 199627097  
TI Chronic opiod treatment induces adenylyl cyclase V superactivation.  
Involvement of G(beta.gamma.).  
AU Avidor-Reiss T.; Nevo I.; Levy R.; Pfeuffer T.; Vogel Z.  
CS Department of Neurobiology, Weizmann Institute of Science, 76100 Rehovot, Israel  
SO Journal of Biological Chemistry, (1996) 271/35 (21309-21315).  
ISSN: 0021-9258 CODEN: JBCHA3  
CY United States  
DT Journal; Article  
FS 005 General Pathology and Pathological Anatomy  
008 Neurology and Neurosurgery  
029 Clinical Biochemistry  
040 Drug Dependence, Alcohol Abuse and Alcoholism  
LA English  
SL English  
AB It has been known for some time that chronic treatment of \*\*\*neural\*\*\* cells and tissues with opioids, contrary to their acute effect, leads to an increase in cAMP accumulation. This phenomenon, defined as adenylyl cyclase superactivation, has been implicated in opiate addiction, yet the mechanism by which it is induced remains unclear. Here, we show that this phenomenon can be reproduced and studied in COS-7 cells cotransfected with adenylyl cyclase type V and .mu.-opioid receptor cDNAs. These cells

display acute opiod inhibition of adenylyl cyclase activity, whereas prolonged exposure to the .mu.-agonist morphine or [D-Ala2, N-methyl-Phe4, Gly-o15]enkephalin leads to a time-dependent superactivation of adenylyl cyclase. This superactivated state is reversible, because it is gradually lost following agonist withdrawal. Adenylyl cyclase superactivation can be prevented by pertussis \*\*\*toxin\*\*\* pretreatment, indicating the involvement of G(i/o) proteins, or by cotransfection with the carboxyl terminus of beta.-adrenergic receptor kinase or with alpha.-\*\*\*transducin\*\*\* (scavengers of G(beta.gamma.) dimers), indicating a role for the G protein. beta.gamma. dimers in adenylyl cyclase superactivation. However, contrary to several other G(beta.gamma.) dependent signal \*\*\*transduction\*\*\* mechanisms (e.g. the extracellular signal-regulated kinase 2/MAP kinase pathway), adenylyl cyclase superactivation is not affected by the Ras dominant negative mutant N17-Ras.

L11 ANSWER 10 OF 12 MEDLINE DUPLICATE

AN 94037127 MEDLINE  
DN 94037127  
TI Metabolic mapping with cellular resolution: c-fos vs. 2-deoxyglucose.  
AU Sharp F R; Sagar S M; Swanson R A  
CS Department of Neurology, University of California at San Francisco, NC  
NC NS27864 (NINDS)  
NS27488 (NINDS)  
SO CRITICAL REVIEWS IN NEUROBIOLOGY, (1993) 7 (3-4)  
205-28. Ref: 159  
Journal code: CRR. ISSN: 0892-0915.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, ACADEMIC)  
LA English  
FS Priority Journals  
EM 199402  
AB 2-Deoxyglucose (2DG) studies have been most useful in mapping activated regions of the nervous system. Cellular localization studies using 2DG have been less rewarding, but results are consistent with current views that increases of 2DG accumulation produced by synaptic activation represent increases in glycolytic glucose metabolism occurring mainly in presynaptic \*\*\*neural\*\*\* and possibly glial elements. Immediate early genes (IEGs), including the fos, jun, and NGFI-A families,

are induced by a wide variety of intracellular signaling pathways. The nuclear localization of the protein products of these genes and their induction by a variety of stimuli make them useful in metabolic activation studies carried out at the cellular level. IEGs have been induced in neurons by osmotic, bacterial endotoxin, steroids, stress, and other hormonal stimuli; by light, auditory, painful, and other sensory stimuli; during stimulation of motor cortex and other motor behaviors; and by various drugs and \*\*\*toxins\*\*\* that act on a variety of neurotransmitter systems, including dopamine and glutamate. In addition, the localization of c-fos gene expression identifies cells that respond to growth factors in \*\*\*vivo\*\*\*. Retinal Muller cells, the major glial cell type of the retina, demonstrate nuclear Fos immunostaining after the intravitreal injection of epidermal growth factor (EGF) or growth factor-alpha (TGF-alpha). This observation demonstrates that adult glia can respond to these growth factors in \*\*\*vivo\*\*\*. The investigation of early response gene expression may be particularly useful for elucidating the role of trophic factors in the cellular response to central nervous system injury.

L11 ANSWER 11 OF 12 MEDLINE  
AN 90150622 MEDLINE  
DN 90150622  
TI Small molecular weight GTP-binding proteins and signal \*\*\*transduction\*\*\*  
AU Yamamoto K; Tanimoto T; Kim S; Kikuchi A; Takai Y  
CS Department of Biochemistry, Kobe University School of Medicine, Japan.  
SO CLINICA CHIMICA ACTA, (1989 Dec 15) 185 (3) 347-55.  
Journal code: DCC. ISSN: 0009-8981.  
CY Netherlands  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199005  
AB We have separated multiple GTP-binding proteins (G proteins) having Mr values of about 20,000 (small Mr G proteins) from bovine brain membranes, purified to near homogeneity and characterized two novel G proteins designated as smg p25A and smg p21, the c-Ki-ras protein (c-Ki-ras p21) and the two rho proteins (rho p20 and rho p21). smg p25A is present

abundantly in brain and adrenal medulla. This G protein is also found in rat pheochromocytoma PC-12 cells, and its mRNA level increased after differentiation of the cells into neuron-like cells in response to nerve growth factor or dibutyryl cyclic AMP. These results suggest that smg p25A plays an important role in the regulation of \*\*\*neural\*\*\* functions. In contrast, smg p21 is found in most tissues. This G protein has the same putative effector domain as ras p21s, suggesting that smg p21 exerts the actions similar and/or antagonistic to those of ras p21s. In fact, smg p21 has been found to be identical with the protein encoded by the Krev-1 gene recently isolated as a gene suppressing the \*\*\*transforming\*\*\* action of Ki-ras p21 in NIH/3T3 cells. On the other hand, rho p20 and rho p21 are ADP-ribosylated by an ADP-ribosyltransferase contained or contaminated in botulinum \*\*\*toxin\*\*\* type C1, presumably C3. Botulinum ADP-ribosyltransferase C3 has recently been shown to induce morphological changes similar to those induced by ras p21 in fibroblasts. Thus, small Mr G proteins are part of a huge network of intracellular regulatory systems and play important roles in the regulation of various cell functions including cell \*\*\*transformation\*\*\*, proliferation and differentiation.

L11 ANSWER 12 OF 12 MEDLINE DUPLICATE  
4  
AN 90040817 MEDLINE  
DN 90040817  
TI Differentiation of PC12 cells with v-src: comparison with nerve growth factor.  
AU Rausch D M; Dickens G; Doll S; Fujita K; Koizumi S; Rudkin B; Tocco M; Eiden L E; Guroff G  
CS Unit on Molecular and Cellular Neurobiology, National Institute of Mental Health, Bethesda, MD 20892.  
SO JOURNAL OF NEUROSCIENCE RESEARCH, (1989 Sep) 24 (1) 49-58.  
Journal code: KAC. ISSN: 0360-4012.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199002  
AB The PC12 rat pheochromocytoma cell line is used extensively as

a model to study \*\*\*neural\*\*\* differentiation. These cells resemble adrenal chromaffin cells, differentiating both morphologically and biochemically when cultured in the presence of dexamethasone, but develop a sympathetic neuron-like phenotype when cultured in the presence of nerve growth factor. Expression of the protein product of the v-src \*\*\*oncogene\*\*\* in PC12 cells also induces neurite outgrowth similar to that resulting from nerve growth factor treatment (Alena et al: Nature 316:557-559, 1985). It is thus possible that c-src or a src-like tyrosine kinase participates in the signal \*\*\*transduction\*\*\* pathway by which nerve growth factor acts on PC12 cells. In this study a temperature-sensitive v-src gene has been introduced into PC12 cells. When cultures of these src- \*\*\*transformed\*\*\* cells are switched from the nonpermissive (40 degrees C) to the permissive (37 degrees C) temperature they elaborate neurites. The differentiation induced by src has been compared with that induced by nerve growth factor by determining whether src- \*\*\*transformed\*\*\* PC12 cells at 37 degrees C exhibit the same biochemical alterations as those induced in PC12 cells treated with nerve growth factor. Neurite extension at 37 degrees C in v-src- \*\*\*transformed\*\*\* cells, like NGF-induced differentiation, is accompanied by an increase in the nerve growth factor-inducible large external (NILE) protein. However, neurite extension in v-src- \*\*\*transformed\*\*\* cells is not blocked by the protein kinase inhibitor K-252a, which completely blocks NGF-induced neurite extension. Likewise, EGF receptor down-regulation and the development of saxitoxin and tetanus \*\*\*toxin\*\*\* binding sites are either much reduced or completely absent in src-differentiated compared with NGF-differentiated PC12 cells.

=> s 14  
'AB' IS NOT A VALID FIELD CODE  
L12 57 L4  
=> d 18

(FILE HOME ENTERED AT 09:24:45 ON 21 SEP 2000)

FILE 'MEDLINE' ENTERED AT 09:24:53 ON 21 SEP 2000  
L1 80711 S NEURONAL/AB,BI  
L2 5827 S L1 AND (TRANSFECT? OR TRANSFORM? OR TRANSDUC?)/AB,BI  
L3 180 S L2 AND TOXIN#/AB,BI  
L4 18 S L3 AND VIVO/AB,BI  
L5 9 S L3 AND ONCOGENE/AB,BI  
L6 2 S L5 AND VIVO/AB,BI  
L7 0 S L3 AND TUMORIGENIC AND VIVO/AB,BI  
L8 0 S L3 AND TUMORIGENIC/AB,BI  
L9 2 S L3 AND IMMORTALIZ?/AB,BI  
FILE 'MEDLINE, EMBASE, BIOSIS, INPADOC, CAPLUS' ENTERED AT 09:29:23 ON 21 SEP 2000  
L10 19 S L3 OR L6 OR L7 OR L8 OR L9  
L11 12 DUP REM L10 (7 DUPLICATES REMOVED)  
L12 57 S L4

=> s 112 and transgen?/ab,bi

'AB' IS NOT A VALID FIELD CODE  
L13 0 L12 AND TRANSGEN?/AB,BI

=> dup rem 112

PROCESSING COMPLETED FOR L12  
L14 25 DUP REM L12 (32 DUPLICATES REMOVED)

=> d 1-bib ab

YOU HAVE REQUESTED DATA FROM 25 ANSWERS - CONTINUE? Y(N)?

L14 ANSWER 1 OF 25 EMBASE COPYRIGHT 2000 ELSEVIER  
SCI B.V.DUPLICATE 1  
AN 199378309 EMBASE  
TI Myr-G(2).alpha. and G(o).alpha. subunits restore the efficacy of opioids, clonidine and neurotensin giving rise to antinociception in G-protein knock-down mice  
AU Garzon J.; Rodriguez-Diaz M.; DeAntonio I.; DeFelipe J.; Rodriguez J.R.; Sanchez-Blazquez P.  
CS J. Garzon, Inst. Neurobiol. Santiago Ramon, Consejo Superior, Investigaciones Cientificas, Avd. Doctor Arce 37, E-28002 Madrid, Spain.  
jgarzon@cajal.csic.es  
SO Neuropharmacology, (1999) 38/12 (1861-1873).  
Refs: 47  
ISSN: 0028-3908 CODEN: NEPHBW  
PUJ S 0028-3908(99)00070-2  
CY United Kingdom  
DT Journal; Article  
FS 002 Physiology  
022 Human Genetics  
029 Clinical Biochemistry

030 Pharmacology  
037 Drug Literature Index  
008 Neurology and Neurosurgery  
LA English  
SL English  
AB In mice whose Gi/o-protein function had been impaired by antisense  
'knock-down' or pertussis \*\*\*toxin\*\*\* treatment, icv injection of myr+-G(i)o.alpha. subunits restored the effectiveness of myr+-G(i)o.alpha. subunits. Selectivity was noted in that only beta.-endorphin, morphine, DPDPE, clonidine and neurotensin to produce antinociception. Myr+-G.alpha. subunits of the class of G-proteins actually impaired were more effective than unlike but related myr+-G.alpha. subunits. Selectivity was noted in that only exogenous myr+-G.alpha. subunits affected (enhanced) the activity of agonists in G.alpha.-deficient signalling systems. This treatment had little effect on agonist potency when the impairment resided at the receptor level. The potential of the opioids, clonidine and R-PIA to increase Galpha.-related in vitro hydrolysis of GTP was also re-established after injecting myr+-G(i2).alpha. subunits into G12-knocked-down mice. Myr+-G(i2).alpha. subunits pre-incubated with GTP gamma.S or GDP beta.S before icv injection did not improve the activity of agonists in \*\*\*vivo\*\*\* (antinociception) or in vitro (regulation of low K(m) GTPase). After impairing the function of PKC beta.1 by antisense treatment or with inhibitor HT, the effect of myr+-G.alpha. subunits on agonist potency was prevented. Electron microscope analysis showed the entry of gold-conjugated myr+-G.alpha. subunits into neural cells. These particles were found in the cytoplasm, associated with the plasma membranes of different \*\*\*neural\*\*\* processes and also in synaptic junctions. In cultured neurons and astrocytes myr+-G(i2).alpha.-associated fluorescence was internalised in a dose-dependent manner and distributed in the plasma membrane and cytosol, as well as in nuclei of dividing astrocytes. Thus, G.alpha. subunits in CSF enter into neurons and functionally couple to the receptor-triggered signalling cascade. As G-proteins have been implicated in the pathophysiology of several neural disorders, this finding may be valuable in the therapy of such dysfunctions. Copyright (C) 1999 Elsevier Science Ltd.

L14 ANSWER 2 OF 25 MEDLINE DUPLICATE  
2 AN 1999343779 MEDLINE  
DN 99343779  
TI Chemokine receptor expression and signaling in macaque and human fetal  
neurons and astrocytes: implications for the neuropathogenesis of AIDS.  
AU Klein R S; Williams K C; Alvarez-Hernandez X; Westmoreland S; Force T;  
Lackner A A; Luster A D  
CS AIDS Research Center, Massachusetts General Hospital, Harvard Medical School, Charlestown 02129, USA.. klein.robyn@mh.harvard.edu  
NC AI01519 (NIAID)  
CA69212 (NCI)  
AI40618 (NIAID)  
+  
SO JOURNAL OF IMMUNOLOGY, (1999 Aug 1) 163 (3) 1636-46.

Journal code: IFB. ISSN: 0022-1767.

CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals  
EM 199910  
EW 19991002  
AB Chemokines are believed to play a role in the neuropathogenesis of AIDS through their recruitment of neurotoxin-secreting, virally infected leukocytes into the CNS. Levels of chemokines are elevated in brains of patients and macaques with HIV/SIV-induced encephalitis. The chemokine receptors CCR3, CCR5, and CXCR4 are found on subpopulations of neurons in the cortex of human and macaque brain. We have developed an in vitro system using both macaque and human fetal neurons and astrocytes to further investigate the roles of these receptors in \*\*\*neural\*\*\* response to inflammation. Here we report the presence of functional HIV/SIV coreceptors CCR3, CCR5, and CXCR4 on fetal human neurons and CCR5 and CXCR4 on astrocytes immediately ex \*\*\*vivo\*\*\* and after several weeks in culture. Confocal imaging of immunostained neurons demonstrated different patterns of distribution for these receptors, which may have functional implications. Chemokine receptors were shown to respond to their appropriate chemokine ligands with increases in intracellular calcium that, in the case of neurons, required

predepolarization with KCl. These responses were blocked by neutralizing chemokine receptor in mAbs. Pretreatment of neural cells with pertussis \*\*\*toxin\*\*\* abolished responses to stromal-derived factor-1 alpha, macrophage inflammatory protein-1 beta, and RANTES, indicating coupling of CCR3 and CXCR4 to a Gialpha protein, as in leukocytes. Cultured macaques neurons demonstrated calcium flux response to treatment with recombinant SIVmac239 envelope protein, suggesting a mechanism by which viral envelope could affect \*\*\*neural\*\*\* function in SIV infection. The presence of functional chemokine receptors on neurons and astrocytes suggests that chemokines could serve to link inflammatory and \*\*\*neural\*\*\* responses.

L14 ANSWER 3 OF 25 MEDLINE DUPLICATE  
3 AN 1999192822 MEDLINE  
DN 99192822  
TI Non-viral \*\*\*neural\*\*\* gene delivery mediated by the HC fragment of tetanus \*\*\*toxin\*\*\*.  
AU Knight A; Carvajal J; Schneider H; Coutelle C; Chamberlain S; Fairweather N  
CS Section of Molecular Genetics, ICSM, London, UK.. am.knight@ic.ac.uk  
SO EUROPEAN JOURNAL OF BIOCHEMISTRY, (1999 Feb) 259 (3) 762-9.  
Journal code: EMZ. ISSN: 0014-2956.  
CY GERMANY: Germany, Federal Republic of  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals; Cancer Journals  
EM 199906  
EW 19990604  
AB Many inherited neurological diseases and cancers could potentially benefit from efficient targeted gene delivery to neurons of the central nervous system. The nontoxic fragment C (HC) of tetanus \*\*\*toxin\*\*\* retains the specific nerve cell binding and transport properties of tetanus holotoxin. The HC fragment has previously been used to promote the uptake of attached proteins such as horseradish peroxidase, beta-galactosidase and superoxide dismutase into \*\*\*neural\*\*\* cells in vitro and in \*\*\*vivo\*\*\*. We report the use of purified recombinant HC

fragment produced in yeast and covalently bound to polylysine [poly(K)] to enable binding of DNA. We demonstrate that when used to cells, this construct results in nonviral gene delivery and marker gene expression in vitro in N18 RE 105 cells (a neuroblastoma x glioma mouse/rat hybrid cell line) and P98 (a glioma cell line).  
 \*\*\*Transfection\*\*\* was dependent on HC and was \*\*\*neutroal\*\*\* cell type specific. HC may prove a useful targeting ligand for future \*\*\*neutroal\*\*\* gene therapy.

L14 ANSWER 4 OF 25 MEDLINE DUPLICATE  
 AN 1999198837 MEDLINE  
 DN 99198837  
 TI Melatonin receptor potentiation of cyclic AMP and the cystic fibrosis transmembrane conductance regulator ion channel.  
 AU Nelson C S; Marino J L; Allen C N  
 CS Center for Research on Occupational and Environmental Toxicology.  
 Department of Psychiatry, Oregon Health Sciences University, Portland 97201, USA.  
 NC AG10794 (NIA)  
 SO JOURNAL OF PINEAL RESEARCH, (1999 Mar) 26 (2) 113-21.  
 Journal code: JND. ISSN: 0742-3098.

CY Denmark  
 DT Journal Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199907  
 EIV 19990704  
 AB We have used the cystic fibrosis transmembrane conductance regulator (CFTR) Cl- channel as a model system to study the cAMP signal \*\*\*transduction\*\*\* pathways coupled to the Xenopus melatonin receptor.  
 During forskolin (Fsk) stimulation, melatonin reduced the amplitude of the CFTR currents in oocytes injected with in vitro transcribed cRNAs for the Xenopus melatonin receptor and CFTR. Pertussis (Ptx) treatment eliminated melatonin inhibition of Fsk stimulated CFTR currents.  
 In oocytes injected with cRNA for melatonin receptors, serotonin (5-HT), and CFTR Cl- channels, application of melatonin together with serotonin (5-HT) activated an additional inward current showing potentiation of adenylyl cyclases by melatonin receptors.  
 Subthreshold

activation of 5-HT7 receptors was sufficient and necessary to permit activation of CFTR channels by melatonin. Preexposure to desensitized the melatonin receptor mediated response. Therefore, based on this model system, the effects of melatonin in \*\*\*vivo\*\*\* could be either positive or negative modulation of other \*\*\*neutroal\*\*\* inputs, depending on the mode of adenylyl cyclase stimulation.

L14 ANSWER 5 OF 25 MEDLINE  
 AN 1999253888 MEDLINE  
 DN 99253888  
 TI GDNF: a novel factor with therapeutic potential for neurodegenerative disorders.  
 AU Walton K M  
 CS Department of Neurobiology, Cephalon, Inc., West Chester, PA 19380, USA.  
 SO MOLECULAR NEUROBIOLOGY, (1999 Feb) 19 (1) 43-59.  
 Journal code: AH6. ISSN: 0893-7648.

CY United States  
 DT Journal Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199908  
 AB The identification of novel factors that promote \*\*\*neutroal\*\*\* survival could have profound effects on developing new therapeutics for neurodegenerative disorders. Glial cell line-derived neurotrophic factor (GDNF) is a novel protein purified and cloned based on its marked ability to promote dopaminergic \*\*\*neutroal\*\*\* function. GDNF, now known to be the first identified member of a family of factors, signals through the previously known receptor tyrosine kinase, Ret. Unlike most ligands for receptor tyrosine kinases, GDNF does not bind and activate Ret directly, but requires the presence of GPI-linked coreceptors. There are several coreceptors with differing affinities for the GDNF family members. The profile of coreceptors in a cell may determine which factor preferentially activates Ret. In \*\*\*vivo\*\*\* differences in localization of the GDNF family members, its coreceptors and Ret suggest this ligand/receptor interaction has extensive and multiple functions in the CNS as well as in peripheral tissues. GDNF promotes survival of several

\*\*\*neutroal\*\*\* populations both in vitro and in \*\*\*vivo\*\*\*. Dopaminergic \*\*\*neutroal\*\*\* survival and function are preserved by GDNF in \*\*\*vivo\*\*\* when challenged by the \*\*\*toxins\*\*\* MPTP and 6-hydroxydopamine. Furthermore, GDNF improves the symptoms of pharmacologically induced Parkinson's disease in monkeys. Several neuron populations isolated in vitro are also rescued by GDNF. In \*\*\*vivo\*\*\*, GDNF protects these neurons from programmed cell death associated with development and death induced by \*\*\*neutroal\*\*\* transfection. These experiments suggest that GDNF may provide therapeutic opportunities in several neurodegenerative disorders.

L14 ANSWER 6 OF 25 EMBASE COPYRIGHT 2000 ELSEVIER  
 SCI B V DUPLICATE 5  
 AN 1998173146 EMBASE  
 TI ABT-594 [(R)-5-(2-Azetylthiomethoxy)-2-Chloropyridine]: A novel, orally effective analgesic acting via \*\*\*neutroal\*\*\* nicotinic acetylcholine receptors: I. In vitro characterization.  
 AU Donnelly-Roberts D L.; Puttfarcken P S.; Kuntzweiler T A.; Briggs C A.; Anderson D J.; Campbell J E.; Plattoni-Kaplan M.; McKenna D G.; Wasiak J. T.; Holladay M W.; William M.; Americ S P.  
 CS Dr D.L. Donnelly-Roberts, NUDR, Building AP10, Dept. 47W, 100 Abbott Park Rd., Abbott Park, IL 60064-3500, United States  
 SO Journal of Pharmacology and Experimental Therapeutics, (1998) 285/2 (777-786).  
 Refs: 45  
 ISSN: 0022-3565 CODEN: JPETAB  
 CY United States  
 DT Journal Article  
 FS 008 Neurology and Neurosurgery  
 024 Anesthesiology  
 030 Pharmacology  
 037 Drug Literature Index  
 LA English  
 SL English  
 AB The discovery of (-)-epibatidine, a naturally occurring \*\*\*neutroal\*\*\* nicotinic acetylcholine receptor (nAChR) agonist with antinociceptive activity 200-fold more potent than that of morphine, has renewed interest in the potential role of nAChRs in pain processing.  
 However, (-)-epibatidine has significant side-effect liabilities associated with potent activity at the ganglionic and neuromuscular junction nAChR subtypes which limit its potential as a clinical

entity.  
 ABT-594 ((R)-5-(2-azetidinylmethoxy)-2-chloropyridine) is a novel, potent cholinergic nAChR ligand with analgesic properties (see accompanying paper by Bannan et al., 1998b) that shows preferential selectivity for \*\*\*neuronal\*\*\* nAChRs and a consequently improved in \*\*\*vivo\*\*\* side-effect profile compared with (+)-epibatidine. ABT-594 is a potent inhibitor of the binding of [3H](+)-cytisine to alpha.4 beta.2 \*\*\*neuronal\*\*\* nAChRs (K(i) = 37 pM, rat brain; K(i) = 55 pM, \*\*\*transfected\*\*\* human receptor). At the alpha.1 beta.1 delta.1 gamma.1 neuromuscular nAChR labeled by [125I] alpha.-bungarotoxin\*\*\* (alpha.-Btx), ABT-594 has a K(i) value of 10,000 nM resulting in a greater than 180,000-fold selectivity of the compound for the \*\*\*neuronal\*\*\* alpha.4 beta.2 nAChR. In contrast, (+)-epibatidine has K(i) values of 70 pM and 2.7 nM at the alpha.4 beta.2 and alpha.1 beta.1 gamma.1 delta.1 nAChRs, respectively, giving a selectivity of only 38-fold. The S-enantiomer of ABT-594, A-98593 has activity at the \*\*\*neuronal\*\*\* alpha.4 beta.2 nAChR identical with ABT-594 (K(i) = 34-39 pM), which demonstrates a lack of stereospecific binding similar to that reported previously for (+)-epibatidine. A similar lack of stereoselectivity is seen at the human alpha.7 receptor. However, A-98593 is 3-fold more potent at the neuromuscular nAChR (K(i) = 3420 nM) and the brain alpha.-Btx-sensitive nAChR (K(i) = 4620 nM) than ABT-594. ABT-594 has weak affinity in binding assays for adrenoceptor subtypes alpha-1B (K(i) = 890 nM), alpha-2B (K(i) = 597 nM) and alpha-2C (K(i) = 342 nM), and it has negligible affinity (K(i) > 1000 nM) for approximately 70 other receptors, enzyme and transporter binding sites. Functionally, ABT-594 is an agonist. At the \*\*\*transfected\*\*\* human alpha.4 beta.2 \*\*\*neuronal\*\*\* nAChR (K177 cells), with increased 8GRb+ efflux as a measure of cation efflux, ABT-594 had an EC50 value of 140 nM with an intrinsic activity (IA) compared with (-)-nicotine of 130%; at the nAChR subtype expressed in IMR-32 cells (sympathetic ganglion-like), an EC50 of 340 nM (IA = 126%); at the F11 dorsal root ganglion cell line (sensory ganglion-like), an EC50 of 1220 nM (IA = 71%); and via direct measurement of ion currents, an EC50 value of 56,000 nM (IA = 83%) at the human alpha.7 homooligomeric nAChR produced in oocytes. A-98593 is 2- to 3-fold more potent and displays approximately 50% greater intrinsic activity than ABT-594 in all four functional assays. In terms of potency, ABT-594 is 8- to 64-fold less active than (+)-epibatidine and also has less IA in these functional assays. ABT-594 (30 muM) inhibits the release of calcitonin gene-related peptide from C-fibers terminating in the dorsal horn of the spinal cord, an effect mediated via nAChRs. Pharmacologically, ABT-594 has an in vitro profile distinct from that of the prototypic nicotine analgesic (+)-epibatidine, with the potential for substantially reduced side-effect liability and, as such, represents a potentially novel therapeutic approach to pain management.

L14 ANSWER 7 OF 25 MEDLINE  
 AN 1998082844 MEDLINE  
 DN 98082844  
 TI Contributions of N-linked glycosylation to the expression of a functional alpha.7-nicotinic receptor in Xenopus oocytes.  
 AU Chen D; Dang H; Patrick J W  
 CS Division of Neuroscience, Baylor College of Medicine, Houston, Texas 77030, USA.  
 NC NS13546 (NINDS)  
 DA04077 (NIDA)  
 SO JOURNAL OF NEUROCHEMISTRY, (1998 Jan) 70 (1) 349-57.  
 Journal code: JAV. ISSN: 0022-3042.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 19980401  
 EW 19980401  
 AB The alpha.7 subunit of the \*\*\*neuronal\*\*\* nicotinic acetylcholine receptor, when expressed in Xenopus oocytes, forms homooligomeric ligand-gated ion channels that are blocked by a snake \*\*\*toxin\*\*\* the alpha.7 sequence has three consensus sites for asparagine-linked glycosylation (N46DS, N90MS, and N133AS). In this study, we show that alpha.7 expressed either in \*\*\*vivo\*\*\* or in vitro is a glycoprotein of 57 kDa. In addition, we demonstrate by site-directed mutagenesis that all three consensus sites are used for glycosylation. To elucidate the role(s) of asparagine-linked glycosylation in the formation and function of the alpha.7 receptor, wild-type and glycosylation-deficient alpha.7 subunits were expressed in COS cells and oocytes. We examined biochemical and physiological properties of expressed receptors and found that glycosylation mutations do not affect homooligomerization and protein expression of the alpha.7 receptor but do affect surface expression of alpha-bungarotoxin binding sites and the function of the receptor. Our data indicate that asparagine-linked glycosylation is required for the expression of a functional alpha.7 receptor in oocytes.

L14 ANSWER 8 OF 25 MEDLINE  
 AN 1998453369 MEDLINE  
 DN 98453369  
 TI Landmarks in the application of 13C-magnetic resonance spectroscopy to studies of \*\*\*neuronal\*\*\* /glial relationships.  
 AU Bachelard H  
 CS MR Centre, Department of Physics, University of Nottingham, UK.  
 ppzwkp@ppm1.not.ac.uk  
 SO DEVELOPMENTAL NEUROSCIENCE, (1998) 20 (4-5) 277-88. Ref: 70  
 Journal code: ECS. ISSN: 0378-3866.  
 CY Switzerland  
 DT (LECTURES)  
 General Review; (REVIEW)  
 (REVIEW, TUTORIAL)  
 LA English  
 FS Priority Journals  
 EM 19990301  
 EW 19990301  
 AB The development of the use of carbon isotopes as metabolic tracers is briefly described. 13C-labelled precursors (13CO2, 13CH4) first became available in 1940 and were studied in microorganisms, but their use was limited by very low enrichments and lack of suitable analytical equipment. More success was achieved with 11C and especially 14C, as these radioactive tracers did not need to be highly enriched. Although the stable 13C isotope can be used at a low percentage enrichment in mass spectrometry, its application to magnetic resonance spectroscopy (MRS) requires very highly enriched precursors, due to its low natural abundance and low sensitivity. Despite such limitations, however, the great

advantage of <sup>13</sup>C-MRS lies in its exquisite chemical specificity, in that labelling of different carbon atoms can be distinguished within the same molecule. Effective exploitation became feasible in the early 1970s with the advent of stable instruments, Fourier **\*\*\*transform\*\*\*** <sup>13</sup>C-MRS, and the availability of highly enriched precursors. Reports of its use in brain research began to appear in the mid-1980s. The applications of <sup>13</sup>C isotopomer analysis to research on **\*\*\*neuronal\*\*\*** /glial relationships are reviewed. The presence of neighbouring <sup>13</sup>C-labelled atoms affects the appearance of the resonances (splitting due to C-C coupling), and so allows for unique quantification of rates through different and possibly competing pathways. Isotopomer patterns in resonances labelled from a combination of [1-<sup>13</sup>C]glucose and [1, 2-<sup>13</sup>C]lactate have revealed aspects of **\*\*\*neuronal\*\*\*** /glial metabolic trafficking on depolarization and under hypoxic conditions in vitro. This approach has now been applied to **\*\*\*vivo\*\*\*** studies on inhibition of glial metabolism using fluoracetate. The results confirm the glial specificity of the **\*\*\*toxin\*\*\*** and demonstrate that it does not affect entry of acetate. When the glial TCA cycle is inhibited, the ability of the glia to participate in the glutamate/glutamine cycle remains unimpaired, in that labelling of glutamine, which can only be derived from **\*\*\*neuronal\*\*\*** metabolism of glucose, persists. The results also confirmed earlier evidence that part of the GABA transmitter pool is derived from glial glutamine.

L14 ANSWER 9 OF 25 BIOSIS COPYRIGHT 2000 BIOSIS  
 AN 1999:107853 BIOSIS  
 DN PREV199900107853  
 TI Congener-specific distribution of polychlorinated biphenyls in brain regions, blood, liver, and fat of adult rats following repeated exposure to Aroclor 1254.  
 AU Kodavanti, Prasada Rao S. (1); Ward, Thomas R. (1); Derr-Yellin, Ethel C.  
 (1); Mundy, William R. (1); Casey, Ann C.; Bush, Brian; Tilson, Hugh A.  
 CS (1) Neurotoxicology Div., National Health Environmental Effects Res. Lab., U.S. Environmental Protection Agency, Research Triangle Park,

NC 27711 USA  
 SO Toxicology and Applied Pharmacology, (Dec., 1998) Vol. 153, No. 2, pp. 199-210.  
 ISSN: 0041-008X.  
 DT Article  
 LA English  
 AB Our previous in vitro studies with both isolated organelles and primary **\*\*\*neuronal\*\*\*** cell cultures found that intracellular signal **\*\*\*transduction\*\*\*** can be perturbed by some noncoplanar PCBs at exposure levels of gforeq 10 mM. However, it is not clear whether such concentrations are achievable in brain in **\*\*\*vivo\*\*\***. Also, the pattern of congener disposition and quantities of the PCB accumulation in tissues of animals exposed to commercial PCB mixtures is not well studied. In the present study, we have conducted PCB congener-specific analysis in different brain regions, liver, blood, and fat of adult male Long-Evans rats dosed orally with Aroclor 1254 (O or 30 mg/kg/day; once per day, 5 days/week for 4 weeks) in corn oil. Twenty-four hours after the last dose, rats were euthanized, and the brains were removed and dissected to obtain cerebellum, frontal cortex, and striatum. Liver, blood, and fat samples were also collected at the same time. Congener-specific analysis of PCBs was performed by high-resolution gas chromatography with electron capture detection. While PCB concentrations in control rat brain regions were less than 0.02 ppm, total PCB congeners in treated animals accumulated to much higher levels. Total levels in the frontal cortex, cerebellum, and striatum were 15.1 +/- 0.3, 13.1 +/- 1.7, and 8.2 +/- 2.6 ppm, respectively. The levels of PCBs in the fat, liver, and blood were 0.041, 0.002, and 0.001 ppm in control rats and 552, 38.3, and 1.6 ppm in treated rats, respectively. In addition to the differential total uptake between tissues, there was differential accumulation of PCBs with respect to the number of chlorines. In all the tissues, the more lightly chlorinated (tetra- and penta-) congeners accumulated less than their respective heavily chlorinated (hexa- to nona-) congeners accumulated more than the proportion of these congeners found in Aroclor 1254 mixture. This shift toward accumulation of heavily chlorinated congeners seems to be more pronounced in the brain than liver and fat. Predominant congeners

(5-32% of total PCBs) detected in different brain regions, blood, liver, and fat are: 2,3,3',4',5,6- (no. 163) + 2,2,3,4,4',5- (no. 138) (coeluted); 2,2',4,4',5,5'- (no. 153) + 2,2',3,3',4,6'- (no. 132) (coeluted); 2,3,3',4,4',5- (no. 156) + 2,2',3,3',4,4',6'- (no. 171) (coeluted); 2,3',4,4',5- (no. 118); 2,2',4,4',5- (no. 99); and 2,3',4,4'- (no. 105). These congeners together accounted for about two thirds of the total PCB load in brain. AU these predominant congeners are ortho-substituted and therefore are noncoplanar in nature. The total PCB concentrations accumulated in brain were as high as 50 IAM (based on average molecular weight of 326.4 for Aroclor 1254) and, at these concentrations, intracellular second messengers were significantly affected in **\*\*\*neuronal\*\*\*** cultures and brain homogenate preparations in vitro. These results indicate that concentrations that altered Ca<sup>2+</sup> disposition and second messenger systems in vitro are achievable in brain in **\*\*\*vivo\*\*\*** following repeated exposure.

L14 ANSWER 10 OF 25 MEDLINE DUPLICATE  
 7  
 AN 1999126974 MEDLINE  
 DN 99126974  
 TI Pituitary adenylate cyclase activating peptide (PACAP) in the retinohypothalamic tract: a daytime regulator of the biological clock.  
 AU Hammibal J; Ding J M; Chen D; Fahrenkrug J; Larsen P J; Gillette M U; Mikkelsen J D  
 CS Department of Clinical Biochemistry, Bispebjerg Hospital, University of Copenhagen, Denmark. biochbbh@inet.uni2.dk  
 NC NS22155 (NINDS)  
 SO ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (1998 Dec 11) 865 197-206.  
 Journal code: SNM. ISSN: 0077-8923.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals; Cancer Journals  
 EM 199904  
 EW 19990403  
 AB The retinohypothalamic tract (RHT) relays photic information from the eyes to the brain biological clock in the suprachiasmatic nucleus (SCN). Activation of this pathway by light plays a role in adjusting circadian timing to light exposure at night. Here we report a new signaling pathway by which the RHT regulates circadian timing in the daytime as well. Using dual-immunocytochemistry for PACAP and the in **\*\*\*vivo\*\*\*** tracer

Cholera \*\*\*toxin\*\*\* subunit B (ChB), intense PACAP immunoreactivity (PACAP-IR) was observed in retinal afferents at the rat SCN as well as in the intergeniculate leaflet (IGL) of the thalamus. This PACAP-IR was nearly lost upon bilateral eye enucleation. PACAP afferents originated from ganglion cells distributed throughout the retina. The phase of circadian rhythm measured as SCN \*\*\*neuronal\*\*\* activity in vitro was significantly advanced by application of PACAP-38 during the subjective day, but not at night. The effect is channelled to the clock via a PACAP 1 receptor-cAMP signaling mechanism. Thus, in addition to its role in nocturnal regulation by glutamatergic neurotransmission, the RHT can adjust the biological clock by a PACAP-cAMP-dependent mechanism during the daytime.

L14 ANSWER 11 OF 25 MEDLINE DUPLICATE  
 AN 199066984 MEDLINE  
 DN 99066984  
 TI LIF (AM424), a promising growth factor for the treatment of ALS.  
 AU Kurek J B; Radford A J; Crump D E; Bower J J; Feeney S J; Austin L; Byrne E  
 CS AMRAD Corporation Ltd, Melbourne, Australia.  
 jkurek@amrad.com.au  
 SO JOURNAL OF THE NEUROLOGICAL SCIENCES, (1998 Oct) 160 Suppl 1 S106-13.

Ref: 64

Journal code: JBJ. ISSN: 0022-510X.

CY Netherlands

DT Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)

(REVIEW, TUTORIAL)

LA English

FS Priority Journals

EM 199905

EW 19990503

AB Growth factors are theoretically promising agents for ALS therapy, but

have been disappointing in subcutaneous delivery due to either toxicity or

lack of major efficacy. Leukaemia inhibitory factor (LIF), was named after

its effect on haemopoietic cells, and belongs to a group of cytokines which includes CNTF, IL-6, CT-1, OM and IL-11. All group

members use the

gp130 signal \*\*\*transducing\*\*\* subunit for intracellular

signalling.

but show differences in biological effect. In vitro and in \*\*\*vivo\*\*\* studies on axotomy and nerve crush models demonstrate a powerful effect of LIF in the survival of both motor and sensory neurones, while reducing denervation induced muscle atrophy. Its effects in muscle also include stimulating myoblast proliferation in vitro, and up-regulation after muscle injury. LIF will also stimulate muscle regeneration in \*\*\*vivo\*\*\*

when applied exogenously after injury. In published studies of both axotomy induced \*\*\*neuronal\*\*\* death and in the Wobbler mouse models LIF is active at doses of 10 microg/kg delivered systemically, well below the expected maximum tolerated dose suggested by primate safety studies.

LIF is expressed in low levels by spinal cord neurones with significant up-regulation when the neurones are damaged by BOAA \*\*\*toxin\*\*\*, an excitatory amino acid associated with a form of ALS. This augments other evidence suggesting LIF is a trauma factor playing a role in the injury response of adult \*\*\*neuronal\*\*\* tissue, and may be more effective than related growth factors. Taken together, the data suggests LIF is a physiologically relevant trophic factor with implications in clinical medicine as a therapy for ALS, and a human recombinant form entered human clinical trials during 1998.

L14 ANSWER 12 OF 25 CAPLUS COPYRIGHT 2000 ACS  
 AN 1998:299013 CAPLUS  
 DN 129:39125  
 TI Calcium mobilization and protease-activated receptor cleavage after thrombin stimulation in motor neurons

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retracts neurites. Both these effects are mediated through a G protein-coupled, proteolytically activated receptor for thrombin (PAR-1). Prolonged exposure to thrombin kills neurons via apoptosis that may also involve PAR-1 activation. Increased [Ca2+]i has been a unifying mechanism proposed for cell death in several neurodegenerative diseases. Thrombin-elevated calcium levels may activate intracellular cascades in neurons leading to cell death. Since thrombin mediates its diverse effects on cells through both heterotrimeric and monomeric G proteins, we also explored what effect altering differential G protein coupling would have on the \*\*\*neuronal\*\*\* response to thrombin. We studied calcium mobilization by thrombin in a model motor \*\*\*neuronal\*\*\* cell line, NSC19, using fluorescence image anal. Confirming effects in other \*\*\*neuronal\*\*\* types, thrombin caused dramatic increases in [Ca2+]i levels, both transiently and after prolonged exposure, which involved activation and cleavage of the PAR-1 receptor. Using an enzyme linked immunosorbent assay (ELISA) and dot-blot anal., we found that the N-terminal fragment of PAR-1 was released into the medium after exposure to thrombin. We confirmed that PAR-1 protein and mRNA expression occurred in motor neurons. We found that cholera \*\*\*toxin\*\*\* inhibited thrombin-mediated Ca2+ influx, pertussis \*\*\*toxin\*\*\* did not significantly alter thrombin action, and lovastatin, a small 21-kDa Ras GTPase (Rho) modulator, showed a tendency to reduce the thrombin effect. These data indicate that thrombin-increased [Ca2+]i, sufficient to trigger cell death in motor neurons, might be approached in \*\*\*vivo\*\*\* by modulating thrombin signaling through PAR-1.

L14 ANSWER 13 OF 25 MEDLINE DUPLICATE  
 AN 97218291 MEDLINE  
 DN 97218291  
 TI Pituitary adenylate cyclase-activating peptide (PACAP) in the retinohypothalamic tract: a potential daytime regulator of the biological clock.

clock. prominent actions on various cells, including neurons. As in platelets, thrombin increases [Ca2+]i mobilization in neurons, and also

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Copenhagen, DK-2400 Copenhagen NV, Denmark.  
NC NS22155 (NINDS)  
SO JOURNAL OF NEUROSCIENCE, (1997 Apr 1) 17 (7)  
2637-44.  
Journal code: JDF. ISSN: 0270-6474.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199904  
EW 19990404  
AB The retinohypothalamic tract (RHT) relays photic information from the eyes to the suprachiasmatic nucleus (SCN). Activation of this pathway by light plays a role in adjusting circadian timing via a glutamatergic pathway at night. Here we report a new signaling pathway by which the RHT may regulate circadian timing in the daytime as well. We used dual immunocytochemistry for pituitary adenylate cyclase-activating peptide (PACAP) and the in \*\*\*vivo\*\*\* tracer cholera \*\*\*toxin\*\*\* subunit B and observed intense PACAP-immunoreactivity (PACAP-IR) in retinal afferents in the rat SCN as well as in the intergeniculate leaflet (IGL) of the thalamus. This PACAP-IR in the SCN as well as in the IGL was nearly lost after bilateral eye enucleation. PACAP afferents originated from small ganglion cells distributed throughout the retina. The phase of circadian rhythm measured as SCN \*\*\*neuronal\*\*\* activity in vitro was significantly advanced (3.5 +/- 0.4 hr) by application of 1 x 10<sup>-6</sup> M PACAP-38 during the subjective day [circadian time (CT)-6] but not at night (CT14 and CT19). The phase-shifting effect is channeled to the clock via a PACAP-R1 receptor, because mRNA from this receptor was demonstrated in the ventral SCN by in situ hybridization. Furthermore, vasoactive intestinal peptide was nearly 1000-fold less potent in stimulating a phase advance at CT6. The signaling mechanism was through a cAMP-dependent pathway, which could be blocked by a specific cAMP antagonist, Rp-cAMPS. Thus, in addition to its role in nocturnal regulation by glutamatergic neurotransmission, the RHT may adjust the biological clock by a PACAP/cAMP-dependent mechanism during the daytime.

L14 ANSWER 14 OF 25 MEDLINE  
10

AN 97360054 MEDLINE  
DN 97360054  
TI Neurotoxicity of soluble macrophage products in vitro--influence of dexamethasone.  
AU Flavin M P; Ho L T; Coughlin K  
CS Department of Pediatrics, Queen's University, Kingston, Ontario, Canada.  
SO EXPERIMENTAL NEUROLOGY, (1997 Jun) 145 (2 Pt 1) 462-70.  
Journal code: EQF. ISSN: 0014-4886.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199710  
EW 19971001  
AB When macrophage conditioned medium is added to neurons in vitro, there is a loss of cell membrane integrity, a loss of cell processes, and a large increase in apoptotic neurons. We tested the influence of a potent anti-inflammatory steroid on the interaction between macrophages and neurons. Dexamethasone was applied to macrophages in culture for 24 h while the culture was stimulated with lipopolysaccharide and hypoxia. Conditioned medium was collected after dexamethasone was removed. The dexamethasone pretreated medium was not toxic to hippocampal neurons in contrast to medium from stimulated macrophages not treated with steroid. The dexamethasone effect was concentration dependent. Pretreatment of macrophages with indomethacin and \*\*\*transforming\*\*\* growth factor beta had similar but less impressive effects when compared to dexamethasone. The effect of dexamethasone may have been mediated by inhibiting the synthesis or release of neurotoxic macrophage protein(s), as a combination of medium from steroid pretreated macrophages with medium from non-treated macrophages was not neuroprotective. The \*\*\*toxin\*\*\* (s) did not appear to be tumor necrosis factor alpha or arginase. A role for most neutral proteases was also excluded. We also assessed the consequence of stressing neurons with a mild hypoxic exposure prior to conditioned medium application. Medium from dexamethasone-treated macrophages did not exaggerate hypoxic \*\*\*neuronal\*\*\* injury, unlike medium from non-dexamethasone-treated macrophages. It did not,

however, block the exaggerating effect when coapplied in equal volume with medium from non-treated macrophages. Dexamethasone at 100 nM had no impact when applied directly to neurons while they were being exposed to conditioned medium. This in vitro protection by dexamethasone may be relevant to the demonstrated benefit of glucocorticoids in selected brain and spinal cord conditions. Suspicion of a potential link between this in vitro finding and in \*\*\*vivo\*\*\* CNS injury justifies an assessment of more specific agents acting on macrophage protein synthesis or secretion.

L14 ANSWER 15 OF 25 MEDLINE  
11  
AN 96375823 MEDLINE  
DN 96375823  
TI Vasoactive intestinal polypeptide modulation of nicotinic ACh receptor channels in rat intracardiac neurones.  
AU Cuevas J; Adams D J  
CS Department of Molecular and Cellular Pharmacology, University of Miami, School of Medicine, FL 33101, USA.  
NC HL-35422 (NHLBI)  
HL-07188 (NHLBI)  
SO JOURNAL OF PHYSIOLOGY, (1996 Jun 1) 493 ( Pt 2) 503-15.  
Journal code: JOV. ISSN: 0022-3751.  
CY ENGLAND; United Kingdom  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199705  
AB 1. The effects of vasoactive intestinal polypeptide (VIP) on isolated parasympathetic neurones of rat intracardiac ganglia were examined under voltage clamp using dialysed and perforated patch whole-cell and excised outside-out membrane patch recording configurations. 2. VIP reversibly potentiated nicotinic ACh-evoked whole-cell currents, with half-maximal potentiation (EC50) obtained with 260 pM VIP. However, VIP had no effect on muscarinic ACh-evoked currents, ATP-evoked currents, or depolarization-activated ionic currents in these neurones. 3. VIP-induced potentiation of nicotinic ACh-evoked whole-cell currents was observed following cell dialysis, and was inhibited reversibly by bath application

of the VIP receptor-binding inhibitor L-8-K (5 microM) or the \*\*\*neuronal\*\*\* nicotinic receptor antagonist mecamylamine (3 microM). 4. The signal \*\*\*transduction\*\*\* pathway mediating VIP-induced potentiation of nicotinic ACh-evoked currents involves a guanine nucleotide-binding protein (G-protein) but not cyclic AMP. Intracellular application of 100 microM GDP-beta-S, or pre-incubation of pertussis \*\*\*toxin\*\*\*, inhibited VIP-induced potentiation of ACh-evoked whole-cell currents. 5. In outside-out membrane patches, co-application of ACh (4 microM) and VIP (4 nM) decreased the duration of closings between bursts and clusters of bursts of ACh single-channel activity relative to control (4 microM ACh alone). VIP, however, did not alter single ACh receptor channel current amplitude, duration of closings and openings within a burst, or mean burst duration. 6. VIP-induced modification of nicotinic ACh receptor channel kinetics results in an increase in the open-channel probability which is sufficient to account for the VIP-mediated potentiation of nicotinic ACh-evoked whole-cell currents. 7. The potentiation of nicotinic ACh-evoked currents by VIP is likely to account for the altered \*\*\*neuronal\*\*\* activity observed in the mammalian intracardiac ganglia in \*\*\*vivo\*\*\* and consequent changes in heart rate and cardiac contractility.

L14 ANSWER 16 OF 25 MEDLINE DUPLICATE  
12 AN 97157369 MEDLINE  
DN 97157369  
TI Calcium in suramin-induced rat sensory neuron toxicity in vitro.  
AU Sun X; Windbank A J  
CS Department of Neurology, Mayo Clinic and Mayo Foundation, Rochester, MN 55905, USA.  
NC NS29769 (NINDS)  
SO BRAIN RESEARCH (1996 Dec 2) 742 (1-2) 149-56.  
Journal code: BSL ISSN: 0006-8993.  
CY Netherlands  
DT Journal Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199706  
EW 19970604  
AB Suramin is an experimental chemotherapeutic agent and a neurotoxin which causes a dose-dependent peripheral neuropathy in \*\*\*vivo\*\*\* and

inhibits dorsal root ganglion (DRG) neurite outgrowth in vitro. The mechanism of suramin-induced cyto- and neurotoxicity remains unclear. Calcium is a key signal \*\*\*transducer\*\*\* in cellular responses to a variety of physiological and pathogenic stimuli. In the present study, we have determined the role of calcium in suramin-induced neurotoxicity in dorsal root ganglion neurons in vitro. Suramin-induced inhibition of neurite outgrowth and induction of \*\*\*neuronal\*\*\* cell death were dose-related phenomena. A low level of extracellular calcium significantly reduced suramin-induced inhibition of neurite outgrowth and delayed \*\*\*neuronal\*\*\* cell death in vitro. Nimodipine (100 microM), an L-type voltage-sensitive calcium channel (VSCC) inhibitor, mimicked low calcium medium and protected neurite outgrowth in regular calcium medium supplemented with 300 microM suramin. TMB-8 (100 microM), an inhibitor of intracellular calcium release, failed to protect neurite outgrowth against the \*\*\*toxin\*\*\*. Calmidazolium (10 microM), a potent calmodulin inhibitor, and calpain inhibitor peptide (CIP, 10 microM) protected neurite outgrowth against suramin. The results support the hypothesis that the calcium signaling system is important in suramin-induced neurotoxicity. Influx of extracellular calcium is more important than release of intracellular calcium in causing cell injury in vitro.

L14 ANSWER 17 OF 25 MEDLINE DUPLICATE  
13 AN 95344784 MEDLINE  
DN 95344784  
TI Pertussis \*\*\*toxin\*\*\* specifically inhibits growth cone guidance by a mechanism independent of direct G protein inactivation.  
AU Kindt R M; Lander A D  
CS Department of Biology, Massachusetts Institute of Technology, Cambridge 02139, USA.  
SO NEURON (1995 Jul) 15 (1) 79-88.  
Journal code: AN8 ISSN: 0896-6273.  
CY United States  
DT Journal Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199511  
AB An assay employing patterned laminin substrata was used to screen for compounds that disrupt neurite guidance. One molecule, pertussis

\*\*\*toxin\*\*\*, caused neurites to wander from patterns that normally guided them, yet had no significant effect on rates of neurite outgrowth. Wandering was greatest on patterns requiring frequent guidance (e.g., laminin stripes with periodic gaps). Surprisingly, the B oligomer of pertussis \*\*\*toxin\*\*\*, which lacks the subunit that inactivates G proteins, was equipotent at disrupting neurite guidance. Pertussis \*\*\*toxin\*\*\* probably acts by binding cell surface carbohydrates, since neurites lacking complex-type N-linked oligosaccharides were insensitive to the effects of the \*\*\*toxin\*\*\*. The B oligomer also blocked growth cone collapse induced by a brain membrane-derived factor; such factors are thought to act as repulsive guidance cues in \*\*\*vivo\*\*\*. That a single reagent can inhibit \*\*\*neuronal\*\*\* responses to both attractive and repulsive guidance cues suggests that such cues may share signaling pathways.

L14 ANSWER 18 OF 25 CAPLUS COPYRIGHT 2000 ACS  
AN 1995:951675 CAPLUS  
DN 124:1847  
TI \*\*\*Toxin\*\*\*-mediated transfer and expression of genes in nerve cells  
AU Mueller, G. P.  
CS Sch. of Medicine, Uniformed Services Univ. of the Health Sciences, Bethesda, MD, USA  
SO Report (1994), ARO-27890.1-L.S.; Order No. AD-A290 501, 17 pp. Avail.: NTIS  
From: Gov. Rep. Announce. Index (U. S.) 1995, 95(19), Abstr. No. 19-02,072  
DT Report  
LA English  
AB Receptor-Mediated Gene Transfer In the CNS: A Feasibility Study. This research sought to det. the feasibility of using receptor-mediated gene transfer as a mechanism for introducing the expression of foreign genes in nerve cells. DNA carrier systems were constructed using \*\*\*neuronal\*\*\* ligands that are rapidly internalized by receptor-mediated endocytosis. These proteins, principally wheat germ agglutinin and tetanus \*\*\*toxin\*\*\* C-fragment, were complexed with high expression reporter genes and applied to nerve cells in vitro, and administered in \*\*\*vivo\*\*\* into rats. Uptake and expression of the reporter genes were analyzed by std. enzymic and histochem. procedures. While we have

demonstrated, for the first time, that cells in brain can internalize and express plasmid DNA, there is no evidence that this process can be made specific through the introduction of a receptor-mediated mechanism. The findings indicate that; (1) receptor-mediated uptake and expression does occur in the CNS, and (2) lysosomal degradn. is probably not the basis for our inability to observe expression. From this it may be concluded that receptor-mediated uptake is not an efficient means for directing the expression of foreign genes in nerve cells in \*\*\*vivo\*\*\*

L14 ANSWER 19 OF 25 MEDLINE  
AN 95179327 MEDLINE  
DN 95179327  
TI Fast inhibition of inwardly rectifying K<sup>+</sup> channels by multiple neurotransmitter receptors in oligodendroglia.  
AU Karschin A; Wischmeyer E; Davidson N; Lester H A  
CS Max-Planck-Institute for Biophysical Chemistry, Göttingen, Germany.  
NC GM-29836 (NIGMS)  
SO EUROPEAN JOURNAL OF NEUROSCIENCE, (1994 Nov 1) 6 (11) 1756-64.  
Journal code: BYG. ISSN: 0953-816X.

CY ENGLAND: United Kingdom  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199506  
AB An essential function of myelinating oligodendroglia in the mammalian central nervous system is the regulation of extracellular potassium levels by means of a prominent inwardly rectifying K<sup>+</sup> current. Cardiac and \*\*\*neuronal\*\*\* K<sup>+</sup> inward rectifiers are either activated by hyperpolarizing voltages or controlled by neurotransmitters through the action of receptor-activated G proteins. Neuromodulation of inward rectifiers has not previously been considered as a way to regulate oligodendrocyte function. Here we report the expression of serotonin, somatostatin and muscarinic acetylcholine G protein-coupled receptors in rat brain oligodendrocytes. Activation of these receptors leads to pertussis \*\*\*toxin\*\*\*-sensitive inhibition of inwardly rectifying K<sup>+</sup> channels within < 1 s. By contrast, in the heart and in neurons, similar pathways activate an inwardly rectifying conductance. Thus, transmitter-mediated blockade of inward rectifiers appears to be an oligodendrocyte-specific variation of a common motif for

convergent signalling pathways. In \*\*\*vivo\*\*\*, expression of this mechanism, which may be dependent on neuron-glia signalling, may have a regulatory role in K<sup>+</sup> homeostasis during neuron activity in the central nervous system.

L14 ANSWER 20 OF 25 MEDLINE  
14  
AN 94170397 MEDLINE  
DN 94170397  
TI Platelet-activating factor: a putative neuromodulator and mediator in the pathophysiology of brain injury.  
AU Yue T L; Feuerstein G Z  
CS Department of Cardiovascular Pharmacology, SmithKline Beecham Pharmaceuticals, King of Prussia, PA 19406-0939.  
SO CRITICAL REVIEWS IN NEUROBIOLOGY, (1994) 8 (1-2) 11-24. Ref: 88  
Journal code: CRR. ISSN: 0892-0915.

CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)  
LA English  
FS Priority Journals  
EM 199406  
AB Platelet-activating factor (1-O-hexadecyl-2-acetyl-sn-glycero-3-phosphocholine [PAF]) is a potent lipid autocoid produced by many cell types. PAF is produced by cultured rat cerebellar neurons and human fetal brain cells, and has been extracted from brain tissue. Multiple PAF receptors have been demonstrated in brain tissue. PAF stimulates intracellular Ca<sup>2+</sup> mobilization and phosphatidylinositol (PI) metabolism in \*\*\*transformed\*\*\* \*\*\*neuronal\*\*\* cell lines via the PAF receptor, to which both pertussis \*\*\*toxin\*\*\* (PTX)-sensitive and -insensitive G protein appear to couple. PAF has potent actions on cerebral vessels and cerebral metabolism when administered in \*\*\*vivo\*\*\*.

Direct \*\*\*neuronal\*\*\* effects of PAF, such as inhibition of acetylcholine release, are observed in vitro. Excessive PAF production in pathological states of the nervous system, such as neurotrauma and stroke, has been shown. In multiple studies in rodent and non-rodent models using highly specific and potent PAF antagonists, reversal or prevention of key consequences of brain injury, such as hypoperfusion following ischemia, reperfusion and edema, inflammatory cell accumulation, neurologic/motor

deficits, and \*\*\*neuronal\*\*\* salvage, has been demonstrated. These studies taken together support a role for PAF as an important mediator in the pathophysiology of brain injury.

L14 ANSWER 21 OF 25 EMBASE COPYRIGHT 2000  
ELSEVIER SCI B.V.DUPLICATE 15  
DN 93095396 EMBASE  
TI Nerve growth factor is a potent inducer of proliferation and \*\*\*neuronal\*\*\* differentiation for adult rat chromaffin cells in vitro.

AU Tischler A S.; Riseberg J C.; Hardenbrook M A.; Cherington V. C.  
CS Department of Pathology, Tufts University School of Medicine, 136 Harrison Avenue, Boston, MA 02111, United States  
SO Journal of Neuroscience, (1993) 13/4 (1533-1542).  
ISSN: 0270-6474 CODEN: JNRSDS

CY United States  
DT Journal; Article  
FS 005 General Pathology and Pathological Anatomy  
008 Neurology and Neurosurgery  
021 Developmental Biology and Teratology  
030 Pharmacology  
037 Drug Literature Index

LA English  
SL English  
AB Adult rat chromaffin cells in vitro show a large proliferative response to NGF, followed by \*\*\*neuronal\*\*\* differentiation. Infection of replicating chromaffin cells with a retrovirus carrying the coli. beta - galactosidase (beta-gal) gene demonstrates beta-gal expression in cells that continue to multiply, that differentiate into neurons, and that become static. The effects of NGF on proliferation and differentiation are abolished by the protein kinase inhibitors K252a and staurosporine, and by cholera \*\*\*toxin\*\*\*, an activator of adenylylate cyclase. They are diminished, but not abolished, by high concentrations of dexamethasone. Both cholera \*\*\*toxin\*\*\* alone and phorbol myristate acetate (PMA), an activator of protein kinase C, elicit small and inconsistent mitogenic responses. The responses to PMA cannot be shown to be additive with the effects of NGF. NGF is a known mitogen and neurotogen for chromaffin cells from neonatal rats, but has not previously been believed to affect similarly chromaffin cells from adults. The findings suggest that portions of NGF signaling pathways might continue to be involved in regulating proliferation of adult rat chromaffin cells in

deficits, and \*\*\*neuronal\*\*\* salvage, has been demonstrated. These studies taken together support a role for PAF as an important mediator in the pathophysiology of brain injury.

\*\*\*vivo\*\*\* , and might be constitutively activated in PC12 cells and other adrenal medullary tumors. They further suggest that rat chromaffin cells might be propagated in vitro to obtain large numbers of sympathetic neurons expressing normal or exogenous genes.

L14 ANSWER 22 OF 25 MEDLINE DUPLICATE  
16

AN 94037127 MEDLINE  
DN 94037127  
TI Metabolic mapping with cellular resolution: c-fos vs. 2-deoxyglucose.  
AU Sharp F R; Sagar S M; Swanson R A  
CS Department of Neurology, University of California at San Francisco..  
NC NS27864 (NINDS)  
NS27488 (NINDS)  
SO CRITICAL REVIEWS IN NEUROBIOLOGY, (1993) 7 (3-4)  
205-28. Ref: 159  
Journal code: CRR. ISSN: 0892-0915.

CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, ACADEMIC)

LA English  
FS Priority Journals  
EM 199402  
AB 2-Deoxyglucose (2DG) studies have been most useful in mapping activated regions of the nervous system. Cellular localization studies using 2DG have been less rewarding, but results are consistent with current views that increases of 2DG accumulation produced by synaptic activation represent increases in glycolytic glucose metabolism occurring mainly in presynaptic \*\*\*neuron\*\*\* and possibly glial elements. Immediate

are early genes (IEGs), including the fos, jun, and NGF1-A families, induced by a wide variety of intracellular signaling pathways. The nuclear localization of the protein products of these genes and their induction by a variety of stimuli make them useful in metabolic activation studies carried out at the cellular level. IEGs have been induced in neurons by osmotic, bacterial endotoxin, steroids, stress, and other hormonal stimuli; by light, auditory, painful, and other sensory stimuli; during stimulation of motor cortex and other motor behaviors; and by various drugs and \*\*\*toxins\*\*\* that act on a variety of neurotransmitter systems, including dopamine and glutamate. In addition, the localization

of c-fos gene expression identifies cells that respond to growth factors in \*\*\*vivo\*\*\*. Retinal Muller cells, the major glial cell type of the retina, demonstrate nuclear Fos immunostaining after the intravitreal injection of epidermal growth factor (EGF) or \*\*\*transforming\*\*\* growth factor-alpha (TGF-alpha). This observation demonstrates that adult glia can respond to these growth factors in \*\*\*vivo\*\*\*. The investigation of early response gene expression may be particularly useful for elucidating the role of trophic factors in the cellular response to central nervous system injury.

L14 ANSWER 23 OF 25 MEDLINE  
AN 94191900 MEDLINE  
DN 94191900  
TI In vitro labeling strategies for identifying primary neural tissue and a

\*\*\*neuron\*\*\* cell line after transplantation in the CNS.  
AU Onifer S M; White L A; Whittemore S R; Holets V R  
CS Department of Cell Biology and Anatomy, University of Miami School of Medicine, FL 33136.  
NC NS26887 (NINDS)  
NS07044-16 (NINDS)  
SO CELL TRANSPLANTATION, (1993 Mar-Apr) 2 (2) 131-49.  
Journal code: B02. ISSN: 0963-6897.

CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199407  
AB Potential labels for identifying embryonic raphe neurons and a clonal, neuronally differentiating, raphe-derived cell line, RN33B, in CNS transplantation studies were tested by first characterizing the labels in vitro. The labels that were tested included

4',6-diamidino-2-phenylindole hydrochloride, 1,1'-diiodo-3,3',3'-tetramethylindocarbocyanine perchlorate, the Escherichia coli lacZ gene, Fast Blue, Fluoro-Gold, fluorescein-conjugated latex microspheres, fluorescein isothiocyanate-conjugated or nonconjugated Phaseolus vulgaris leucoagglutinin, methyl o-(6-amino-3'-imino-3H-xanthen-9-yl) benzoate monohydrochloride, or tetanus \*\*\*toxin\*\*\* C fragment. Subsequently, the optimal in vitro labels for embryonic raphe neurons and for RN33B cells were characterized in \*\*\*vivo\*\*\* after CNS transplantation. In vitro, 1,1'-diiodo-3,3',3'-tetramethylindocarbocyanine perchlorate (Dil) optimally labeled embryonic neurons. The Escherichia coli

lacZ gene optimally labeled RN33B cells. Most labels were rapidly diluted in cultures of embryonic astrocytes and proliferating RN33B cells.

Some labels were toxic and were often retained in cellular debris. In \*\*\*vivo\*\*\*, Dil was visualized in transplanted, Dil-labeled raphe neurons, but not in astrocytes up to 1 mo posttransplant. Dil-labeled host cells were seen after transplantation of lysed, Dil-labeled cells. beta-Galactosidase was visualized in transplanted, Escherichia coli gene-labeled RN33B cells after 15 days in \*\*\*vivo\*\*\*. No beta-galactosidase was seen in host cells after transplantation of lysed, lacZ-labeled RN33B cells. The results demonstrate that labels for use in CNS transplantation studies should be optimized for the specific population of donor cells under study, with the initial step being characterization in vitro followed by in \*\*\*vivo\*\*\* analysis. Appropriate controls for false-positive labeling of host cells should always be assessed.

L14 ANSWER 24 OF 25 BIOSIS COPYRIGHT 2000 BIOSIS  
DUPLICATE 17

AN 1992:502612 BIOSIS  
DN BA94:121137  
TI CILIA FROM ABALONE LARVAE CONTAIN A RECEPTOR-DEPENDENT G PROTEIN \*\*\*TRANSDUCTION\*\*\* SYSTEM SIMILAR TO THAT IN MAMMALS.  
AU BAXTER G T; MORSE D E  
CS MARINE BIOTECHNOL. CENT., UNIV. OF CALIFORNIA, SANTA BARBARA, CALIFORNIA 93106.  
SO BIOL BULL (WOODS HOLE), (1992) 183 (1), 147-154.  
CODEN: BIBUBX. ISSN: 0006-3185.

FS BA; OLD  
LA English  
AB Lysine and related diamino acids amplify (facilitate) the response to inducers of metamorphosis in larvae of the marine mollusk *Hydrobia ulvae*. Previous studies showed that a cholera \*\*\*toxin\*\*\*-sensitive G protein \*\*\*transduces\*\*\* the lysine signal via a diacylglycerol-dependent pathway. We have isolated and partially purified larval cilia that may be involved in recognizing the facilitating chemical signals. These isolated cilia provide an open or porous membrane-associated sensory system that is uniquely tractable for in vitro analyses of chemosensory signal \*\*\*transduction\*\*\*. The cilia contain receptors that exhibit sodium-independent binding of the facilitating diamino acids. The binding strength for lysine and related diamino acids in vitro is correlated with the effectiveness of these

ligands as facilitators in \*\*\*vivo\*\*\*. The cilia contain a cholera \*\*\*toxin\*\*\*-sensitive G protein functionally coupled to the lysine receptor. The receptor and the G protein reciprocally regulate one another, suggesting that the chemosensor may be a member of the rhodopsin-like, G-protein-coupled transmembrane receptor superfamily.

Previous analyses of mRNAs from the larval cilia revealed a sequence coding for a G protein with high homology to Gq from mammalian brain, and another sequence coding for a protein homologous to Gi/Go. Similarities between this system, other chemosensory signal \*\*\*transduction\*\*\* pathways, and mechanisms of \*\*\*neuronal\*\*\* long-term potentiation are evident. Because the receptors and \*\*\*transducers\*\*\* controlling settlement and metamorphosis in *Halobates* and other marine invertebrate larvae appear homologous to components controlling \*\*\*neuronal\*\*\* activity, cellular proliferation, and differentiation in mammals, characterization of the molecules controlling metamorphosis may help in the design of new regulators useful in medicine.

L14 ANSWER 25 OF 25 MEDLINE  
 AN 92343492 MEDLINE  
 DN 92343492  
 TI NMDA receptor-mediated arachidonic acid release in neurons: role in signal \*\*\*transduction\*\*\* and pathological aspects.  
 AU Lazarewicz J W; Salinska E; Wroblewski J T  
 CS Fidia-Georgetown Institute for the Neurosciences, Georgetown University  
 SO ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY, (1992) 318 73-89.  
 Journal code: 2LU. ISSN: 0065-2598.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199210  
 AB The N-methyl-D-aspartate (NMDA)-sensitive subtype of glutamate receptor, which gates Ca(2+)-permeable ion channels, is known for its role in learning and memory formation, in the induction of long-term potentiation, and also in seizure activity and neurotoxicity. In primary cultures of cerebellar neurons, agonists of NMDA receptors induce a dose-dependent release of [3H]arachidonic acid ([3H]AA), which is potentiated by activation of the glycine-positive modulatory site and inhibited by NMDA

receptor antagonists. NMDA receptor-induced [3H]AA release is inhibited by quinine and partially depends on the presence of extracellular calcium.

The [3H]AA release is not sensitive, however, to pretreatment with pertussis or cholera \*\*\*toxin\*\*\*, which suggests a Ca(2+)-dependent activation of phospholipase A2 not employing G proteins.

Pretreatment of cultures with the natural and semisynthetic sphingolipids GT1b and PKS 3, respectively, inhibits NMDA receptor-mediated [3H]AA release. We also demonstrated glutamate-evoked [3H]AA release from rat hippocampal slices, which is NMDA receptor mediated, calcium dependent and sensitive to quinine. Arachidonic acid and its metabolites have been shown to play a role as second messengers and to modulate \*\*\*neuronal\*\*\* activity.

Moreover, they are thought to act as transsynaptic modulators in the mechanism of NMDA receptor-induced long-term potentiation in the hippocampus. Their role in ischemic brain pathology has also been postulated. Our experiments on cultured cerebellar granule cells, incubated in a Mg(2+)-free medium deprived of glucose and oxygen, demonstrated a time-dependent stimulation of [3H]AA release. This release was inhibited by antagonists of NMDA receptors and by quinine. Stimulation of NMDA-sensitive glutamate receptors and the subsequent calcium-mediated activation of phospholipase A2 may play a role in the in \*\*\*vivo\*\*\* release of arachidonic acid during brain ischemia.

This hypothesis is supported by the observation that the enhanced level of thromboxane B2 in the gerbil brain after 5 min of global ischemia is reduced by the systemic application of either the NMDA antagonist MK-801 or the ganglioside GM1.

=> d his

(FILE 'HOME' ENTERED AT 09:24:45 ON 21 SEP 2000)

FILE 'MEDLINE' ENTERED AT 09:24:53 ON 21 SEP 2000  
 L1 80711 S NEURONAL/AB.BI  
 L2 5827 S L1 AND (TRANSFECT? OR TRANSFORM? OR TRANSDUC?)/AB.BI  
 L3 180 S L2 AND TOXIN#/AB.BI  
 L4 18 S L3 AND VIVO/AB.BI  
 L5 9 S L3 AND ONCOGENE/AB.BI

L6 2 S L5 AND VIVO/AB.BI  
 L7 0 S L3 AND TUMORIGENIC AND VIVO/AB.BI  
 L8 0 S L3 AND TUMORIGENIC/AB.BI  
 L9 2 S L3 AND IMMORTALIZ?/AB.BI

FILE 'MEDLINE, EMBASE, BIOSIS, INPADOC, CAPLUS' ENTERED AT 09:29:23 ON 21 SEP 2000  
 L10 19 S L5 OR L6 OR L7 OR L8 OR L9  
 L11 12 DUP REM L10 (7 DUPLICATES REMOVED)  
 L12 57 S L4  
 L13 0 S L12 AND TRANSGEN?/AB.BI  
 L14 25 DUP REM L12 (32 DUPLICATES REMOVED)

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FULL ESTIMATED COST	138.05	146.49		

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FULL ESTIMATED COST	0.00	146.49		

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	0.00	-1.11		

STN INTERNATIONAL LOGOFF AT 09:49:02 ON 21 SEP 2000